Chapter 9

LONG-TERM AND LOW-LEVEL EFFECTS OF IONIZING RADIATION

THOMAS L. WALDEN, Jr., Ph.D.*

* *Radiation Biologist, Radiation Biochemistry Department, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145*

INTRODUCTION

Ionizing radiation damages biological tissues by exciting or ionizing their atoms and molecules.[1] Additional indirect damage is caused by the formation of free radicals in water, which makes up 75%-80% of the mass of living systems. The primary products of water radiolysis are the hydroxyl radical, hydrogen radical (hydrogen atom), and hydrated electron; hydroperoxy radicals and hydrogen peroxide are also formed in the presence of oxygen. The production of lysosomal enyzmes and biological mediators, such as histamine and prostaglandins, is another biological response to radiation exposure.[2,3] Depending on the radiation dose and the biochemical processes altered, damage may be prompt (expressed minutes to weeks after exposure) or delayed (expressed several months to years later) (Figure 9-1). Some radiation-induced injuries may not become apparent until they are passed on to succeeding generations.

Radiation doses to biological tissues are measured in three ways. *(a)* The exposure dose of gamma or X rays in air is expressed in *roentgens* (R). *(b)* The dose of any type of radiation absorbed by the tissues was, at one time, expressed by the *rad*, which is equivalent to 100 ergs of energy per gram of tissue. The international measure of absorbed dose is now the *gray* (Gy), which is equal to 100 rads (conversely, 1 rad equals 1 cGy). *(c)* Finally, because the biological responses to radiation exposure may vary with the type of radiation, dose equivalents are expressed by the *rem*, which equals 1 joule per kilogram, or by the *sievert* (Sv), which is an international unit equaling 100 rem. The Sv allows effects from radiations with differing LET values to be compared, since 1 Sv of neutron radiation has the same biological effects as 1 Sv of low-LET gamma or X radiation. Comparisons cannot be made among absorbed-dose measures of different kinds of radiation (for example, 1 Gy of neutron radiation will not have the same effect as 1 Gy of gamma or X radiation).

Low-level radiation exposure is generally considered to be less than the dose that produces immediate or short-term observable biological effects. In the human, low-LET gamma or X radiation doses of less than 0.5 Gy do not produce any prodromal symptoms or the hematopoietic subsyndrome;[4,5] however, low-level radiation exposure does increase the probability that delayed effects will occur.[6-13] Three primary delayed effects—somatic, genetic, and teratogenic[6-9]—can be observed and are already present in the population and in the gene pool.[7,8] Irradiation enhances the naturally occurring frequency of the effect, and in some cases produces the observable end point by a process different from those of natural selection. Certain biological responses have such low thresholds that they are statistically indistinguishable, in many cases, from normal incidence.[7,8,10] Even so, current radioprotection guidelines state that all exposures to radiation should be avoided if possible and that exposure should be kept as low as is reasonably achievable.[14]

BACKGROUND RADIATION

Living organisms are continually exposed to ionizing radiation in nature as well as from nuclear weapons testing, occupations, consumer products, and medical procedures.[7,8,15] The radiation from all of these sources together is called *background radiation*, and is estimated to measure 180-200 mrem/person/year. Medical procedures contribute most whole-body background radiation (Figure 9-2).[7,8] 1 In addition, large doses of partial-body radiation may be delivered to the lung by radon gas (radon-222 and radon-220), produced from the natural decay of radium and thorium.[16] High concentrations of radon gas escape from soil and are released from marble and granite, accumulating in buildings with poor air circulation.[16] Radon exposure is a health concern because its solid daughter products, polonium-214 and -218, decay by alpha-particle emission in the human body near the lung tissue and may increase the incidence of lung cancer.[16]

Extraterrestrial radiation includes solar-flare and cosmic radiation. Most cosmic radiation is absorbed by the dense atmosphere before it reaches the earth's surface. A person's exposure to cosmic radiation increases at higher latitudes or altitudes, as the atmosphere becomes less dense.[7,8] A resident of the higher-altitude city of Denver receives approximately 100 mrem more radiation exposure than does a resident of Washington, D.C. A cross-country airplane flight increases individual exposure by 0.2 mrem/hour because the level of cosmic radiation is greater at 36,000 feet than at sea level.[7] As humans venture farther from the protective atmosphere, either in supersonic air carriers or in spaceflight, their background occupational exposures to cosmic radiation will increase. The British Concorde supersonic transport maintains radiation-monitoring equipment so that it may drop to lower-altitude flight routes if increases in solar or cosmic radiation are detected.[8] Spaceflight increases exposure to solar and cosmic radiations; *Apollo* astronauts traveling to the moon received an average of 275 mrem over 19.5 days.[8]

On earth, naturally occurring radioactive elements contribute to background radiation.[7,8] External exposure sources include potassium-40, which may be concentrated in concrete, and radon gas. Internal radiation comes primarily from radioactive isotopes of naturally occurring elements in biological systems, such as potassium-40 and sodium-24. In some areas of Brazil and India, large concentrations of monazite, a mineral containing thorium, are present in the soil or sand. Background-radiation exposures there range from 0.008 to 0.17 Gy/year.[8]

Fallout from nuclear weapons testing peaked in 1964, after seventy-seven atmospheric detonations occurred in 1962. Of the total fallout, 69% was from carbon-14, 4% was from cesium-137, and 3% was from strontium-90. The remaining 24% was from radioactive isotopes of plutonium, rubidium, barium, iodine, iron, manganese, krypton, americium, tritium, and zinc.[8] Carbon-14 will be a long-term contributor to background radiation because it has a half-life of 5,700 years. Nuclear fallout has decreased because of the total ban on atmospheric testing by

the United States, Great Britain, and the Soviet Union, although several other countries continue atmospheric testing.

Radiation is also emitted from consumer products, such as color television sets (averaging 0.3-1.0 rem/hour of use), video terminals, smoke detectors (which contain an alpha emitter, usually americium-241), and dinnerware that uses uranium for an orange color.[7,15] Ophthalmic glass, used in prescription lenses, contains trace impurities of thorium-232, and uranium is added to dental porcelain to give dentures a natural fluorescent quality.[15] The latter may result in an alpha radiation dose of 60 rem/year to the gums.[15]

SOMATIC EFFECTS

Delayed somatic effects of ionizing radiation result from somatic mutations and accumulated damage, and include impaired circulation, necrosis, fibrosis of skin and muscle tissue, loss of hair, loss of taste, impaired bone growth, susceptibility to disease, immunodeficiency, aplastic anemia, cataracts, and increased incidence of cancer.[6-9,12]

Some organs are more radioresistant than others. Radiation doses exceeding 15-50 Gy must be received before damage to the liver or heart is detected.[6,8] Other tissues, such as the lens and the sperm, show some detriment from doses as low as 0.15-0.30 Gy.[7,8,10,17] Delayed somatic effects of intermediate- or high-level exposures include cataract formation, skin abnormalities, and sterility.

Cataract Formation

The lens tissue of the eye is particularly radiosensitive, and radiation exposure can result in its increased opacity.[7,8,18-22] Radiation cataractogenesis is the most common delayed radiation injury,[21] and is thought to result from damage to the anterior equatorial cells of the lens's epithelial tissue.[23] These cells normally divide and migrate to the posterior portion of the lens, where they gradually lose their nuclei and become lens fibers.[8,23] The lens tissue, like that of the testes and the brain, is separated from the rest of the body by a barrier system.[8] As a result, it has no direct blood supply, no macrophages for phagocytosis, and no way to remove accumulated damage. In a study of 446 survivors of the Nagasaki atomic bomb, 45% of the 395 persons who were 0.1-2.0 km from the hypocenter of the bomb developed cataracts by 1959 (whereas only 0.5%, or 2 out of 395, had severe visual impairment).[19-21] Four of the remaining fifty-one persons (7.8%) who were 2-4 km from the bomb hypocenter developed mild cataract impairment. Even survivors exposed to small doses of radiation were at increased risk for cataract formation. By 1964, the incidence of cataract formation among atomic-bomb survivors who received 0.01-0.99 Gy of radiation was 1.5% in Hiroshima compared to 1.0% in the control population, and 2.0% in Nagasaki compared to 0.9% in controls (Figure 9-3).[22] Higher doses tend to increase the

degree of opacity and shorten the latency period.[7,8] There is a 10% risk of developing a severely impairing cataract following a single exposure to 2.4 Gy of low-LET radiation, and a 50% risk for a dose of 3.1 Gy.[10] The estimated dose for 50% incidence of cataract formation increases from 3.1 Gy to 9.3 Gy by lowering the dose rate or extending the exposure period.[10] The latency period for cataract formation in humans has been estimated to be 6 months to 35 years; however, fractionation or protracted exposure lowers the incidence and prolongs the latency.[7,8]

Small radiation doses may increase the opacity, but visually impairing cataract formation results from an accumulation of dead or injured cells, and therefore has a threshold. For low-LET radiation, this threshold is 2 Gy.[7,8] High-LET neutrons have thresholds of less than 0.2 Gy.

Other parts of the eye are not as radiosensitive as is the lens. The threshold for corneal edema is 10 Gy of low-LET radiation; for atrophy of the lacrimal gland, it is 20 Gy.[8,10] Doses of less than 0.1 Sv/year are not thought to present appreciable risk for detectable visual impairment. The International Commission on Radiological Protection (ICRP) has recommended an occupational exposure limit of 0.15 Sv for the eye.[24]

Sterility

Males. Germ cells of the human testes are very radiosensitive.[7,8,25] Temporary sterility may occur after 0.1-Gy whole-body or local irradiation, with 50% incidence following 0.7 Gy.[7,8,10] Sperm cells become more resistant as they develop; spermatogonia are more radiosensitive than spermatocytes, which are in turn more radiosensitive than spermatids.[26] The regenerating spermatogonial stem cell (A_s) is more radioresistant than the developing spermatogonia (B). The ED_{50} for damage to spermatogonia is 0.11 Gy of low-LET radiation.[27] The spermatid is also fairly radioresistant, requiring X-ray doses of 6 Gy to show visible damage.[26]

Radiogenic aspermia is caused by a maturation-depletion process similar to that observed for hematopoietic cells after irradiation. Radiation kills stem cells or delays mitosis, so that differentiating cells continue to divide without being replaced. The latency period for aspermia after radiation exposure is approximately 2 months,[26] and the time for recovery is several months to years. Chronic and protracted exposures produce greater testicular damage than do acute large exposures. This damage is reflected in the duration of aspermia,[7,8,25] and is thought to result from cycling of the radioresistant A_s spermatogonia to the more radiosensitive B spermatogonia.[7,8,25] A dose of about 0.35 Gy produces a 50% incidence of aspermia after a protracted exposure of 1-10 days.[10] At low dose rates, the recovery period depends on the total dose received: approximately 1 year following a 1-Gy exposure, 3 years for 2-3 Gy, and up to 5 years for 6 Gy.[26] A fractionated dose of 2-3 Gy may require up to 14 years for recovery.[28] Doses of 0.08 Gy do not significantly affect sperm count or alter plasma follicle stimulating

hormone (FSH) levels.[26] Radiation doses of up to 6 Gy do not alter plasma levels of testosterone, but do decrease the levels of urinary hormone. Decreased production of testosterone by the Leydig cells has been observed in humans receiving 6 Gy of X rays. Plasma levels are not affected because there will be a compensating increased number of Leydig cells 3 months after irradiation.[26] Following the onset of aspermia, there is a three- to fourfold increase in urinary gonadotropin, plasma FSH, and luteinizing hormone. Elevated levels return to normal when spermatogenesis resumes.[26]

Permanent male sterility may occur after 2 Gy (local or whole-body exposure) but generally requires doses between 5 and 9.5 Gy.[8] These doses are within the lethal range for whole-body exposure.[7]

Females. The ovary is not as sensitive to radiation-induced temporary sterility as is the testis, but it is more sensitive to permanent sterility[7,8,25] These distinctions are based on differences in the stages of development of the two germ cell groups. Shortly before birth, the oogonia stop multiplying and proceed to prophase I of meiosis.[29] After puberty, meiosis resumes for individual cells by ovulation. Oocytes lose the ability to renew after birth and are unable to replace stem cells that have been damaged or killed by radiation. The oocyte is most radiosensitive as a proliferative stem cell during the fetal stage of gestation, prior to ceasing mitosis and entering meiosis.[7,8]

Temporary sterility may be induced in females by acute radiation doses of 1.5-6.4 Gy.[8,10] Permanent sterility results from doses of 2-10 Gy, and depends on the woman's age at the time of irradiation.[8,10,25] Older women, particularly those close to menopause, are particularly radiosensitive for sterilization. Two Gy of low-LET radiation may result in permanent sterility of 50% of the exposed female population over 40 years of age, compared to an estimated 3.5 Gy for women under 40.[10] This is simply due to the numbers of oocytes present at the time of irradiation.[7,8,25] Women have about one-half million oocytes at puberty, which are almost depleted through atresia at menopause.[29]

Higher radiation doses of 3.6-20.0 Gy are required for sterilization when the exposures are prolonged or fractionated.[8,10] From the 1920s through the 1950s, radiation exposure was occasionally prescribed to treat infertility and sterility.[30] One-third of the women referred for this treatment had amenorrhea. Each woman received a total dose of 0.65 Gy to the ovaries and 0.75 Gy to the pituitary gland, divided in three fractions over 2 weeks. In one study, this technique had a 55 % success rate: 351 of 644 patients treated were able to conceive.[30] The treatment has been discontinued because of the concern for associated risks of genetic and somatic damage. Higher doses of low-LET radiation (1.25 Gy) can result in a delay of the menstrual cycle.[10]

Radiation Effects on Skin and Hair

Soon after Roentgen's discovery of X rays,[31] researchers and radiologists became aware of the skin's sensitivity to radiation damage.[32-26] Eight months after the discovery of X rays in 1896, a German scientist reported a case of dermatitis and alopecia on the face and back of a 17-year-old man who had been exposed to these rays for 10-20 minutes a day for 4 weeks during an investigation.[33] Interestingly, the accompanying erythema, which resembled a burn, was painless, whereas chronic radiation dermatitis following repeated exposure is usually extremely painful.[35-37]

In another 1896 case, a man received an hour-long X-ray exposure during an examination for a kidney stone.[37] The patient experienced nausea (a prodromal symptom) 3 hours after irradiation. Following a second exposure lasting 1.5 hours, the patient developed a radiation sequela leading to ulcer formation at the site of exposure, which was not responsive to skin grafting.

An 1897 case study initiated the popularity of X-radiation treatment for dermatological ailments. A Viennese doctor administered X radiation in two hour-long treatments per day for 10 days to depilate a nevus pilosis birthmark covering the back of a 5-year-old girl.[34] Epilation occurred 11 days after the initiation of treatment.

Before the introduction of the roentgen in 1928 as a unit to measure exposure dose, the *skin erythema dose* (SED) was commonly used.[38] The SED is the radiation dose required to produce a given degree of erythema. It depends on the quality, energy, and exposure time of the radiation. For X radiation, the SED is about 8.5 Gy. In 1925, it was proposed that the exposure of radiologists and X-ray machine operators not exceed 1 /100th of the SED in a 30-day period.[38]

During a radiation incident, skin may be exposed either by direct blast irradiation or by *beta burn* from the direct deposition of particulate fallout.[5,39] The degree of radiation-induced skin damage depends on a number of factors, including the type of radiation; the dose and dose rate; the area of skin irradiated; and skin-quality characteristics, such as texture, age, color, thickness, and location.[7,8,10,40-45] The neck is the most radiosensitive area because its skin is thin and usually not protected by clothing.[46,47] Additional trauma through burn, abrasion, exposure to ultraviolet light, or extreme temperature variations will increase the damage.[45,46,48] Environmental factors or inadequate clothing may contribute to hyperthermia, and wool or other coarse fabrics may further abrade the damaged skin. An illness like diabetes[43] or a genetic disease like ataxia telangiectasia[8,40,44] may also make the skin more radiosensitive. Alpha radiation is of little concern for skin damage because the average penetrated dose is usually absorbed by the dead corneocytes of the stratum corneum. However, it may present a problem at sites where the skin is thinner and the radiation can penetrate to the basal level.[41]

Beta particulates in fallout may contain extremely high radiation dose rates (tens of Gy per hour). When they land on the skin, their energy may penetrate to the germinal basal cells.[5,39,41,49] This radiation damage (beta burn) was observed in the atomic-bomb survivors and the Marshall Islanders (Figure 9-4) who had been exposed to nuclear fallout.[5,39,50,51] The threshold dose of beta radiation for skin damage depends on the average energy of the beta particle, the total absorbed dose, and the dose rate.[49] The average penetrating range of a beta particle is proportional to its energy; thus, higher-energy beta emitters, such as strontium-90 (0.61 MeV average), require lower surface doses to produce wet desquamation than do lower-energy beta particles, such as those from cobalt-60 (0.31 MeV average).[49] The surface threshold doses for transepidermal injury in the skin of pigs is 15 Gy for strontium-90, 40 Gy for cobalt-60, and 200 Gy for sulfur-35.[49] The exposure from each of these radioisotopes delivers approximately the same tissue dose to the basal germ cells. Lower-energy beta particles like sulfur-35 (0.17 MeV energy) are not capable of penetrating to the dermis and cannot induce chronic radiation dermatitis.[49] Beta injuries from fallout can be minimized by decontamination and washing.

Radiation damage to the dermis has a threshold dose of about 20 Gy,[52] with 50% incidence at 60 Gy.[53] Five progressive categories of radiation damage are observed in skin: erythema, transepithelial injury (moist desquamation), ulceration, necrosis, and skin cancer.[32,38-43,45,54]

Radiation-induced erythema occurs in two stages: *(a)* mild initial erythema, appearing usually within minutes or hours on the first day after irradiation (occurring earlier with higher doses), and *(b)* the main erythema, appearing at 2-3 weeks and persisting for longer periods.[10,45,54] In some cases, a third erythema may occur at 6 weeks.[45] Radiation-induced erythema is a threshold phenomenon.[8,45,54] A dose of 6 Gy of low-LET radiation received in less than 1 day, or 10 Gy in 10 days, will induce erythema in 50% of exposed persons.[8,10] The threshold for neutron radiation is 2 Gy.[8] Because of these variables, and the fact that the threshold dose decreases with an increase in the surface area exposed, erythema is not a good biological dosimeter.[8,10,45,49,54] Early erythema arises from the release of mediators and from increased capillary dilation and permeability.[48] It is equivalent to a first-degree burn or mild sunburn, subsiding within 2 or 3 days.[45,54] Although indomethacin or other prostaglandin-synthesis inhibitors have been used topically to prevent or reduce erythema caused by sunburn or ultraviolet light,[52] they have not been widely used to treat radiation-induced erythema. (One study suggested that systemic and topical applications of prostaglandin inhibitors may be useful in minimizing late damage and necrosis from large radiation doses.)[53] When early erythema subsides, it will be latent for 2-3 weeks, depending on the dose.

The second onset of erythema is attributed to impaired circulation in the arterioles and capillaries, producing inflammation and edema[8,45,48] and accompanied by dry desquamation of the epidermal corneocytes. Low radiation doses induce mitotic

delay,[45-55] with subsequent sloughing of epidermal layers. Higher radiation doses extend the duration of mitotic delay but do not alter the rate of cell sloughing at the skin surface. Upper cells are sloughed or abraded off, exposing cells that are not completely keratinized. Cell death and moist desquamation ensue.

Both dry and wet desquamation occur about 1-4 weeks after irradiation.[37,45,54] Regeneration of the stratum corneum requires 2 months to 4 years,[44] and this regenerated tissue will be more sensitive to other skin damaging agents.[45,46] The new skin may be thinner than the original, with greater sensitivity to touch and pain.[45,49] Reduction or loss of the dermal ridges making up the fingerprint has occurred from large or chronic exposures.[45]

Epidermal basal cells are thought to be the targets of early radiation damage,[45,54] and further damage to the surrounding vasculature is an important factor in late radiation injury and necrosis.[8,32,41,45,46] The blood vessel damage may lead to telangiectasia, and fibrosis and alterations in connective tissue may appear.[8,42,45,46] Hyper- or hypopigmentation may occur after radiation exposure: low doses activate melanocytes and produce hyperpigmentation, and higher doses may result in death of melanocytes and hypopigmentation.[45,56]

Dermal necrosis from radiation results from cell death in the dermis, and is equivalent to third-degree thermal burns.[10,42,53] Ulceration is seen with doses greater than 20 Gy;[44] some muscular atrophy may occur with highly penetrating radiation.[44,46] When the proliferation rate of basal cells is depressed for long periods, fibrotic repair may surpass the basal cell repair, leading to reduced tonicity and resiliency and the formation of scar tissue.[44,45] Figure 9-5 shows the general pattern of skin damage of a patient who received large doses of radiotherapy. Ulceration with scar-tissue formation occurs after 30 Gy,[44] and severe fibrosis after 55 Gy.[56] Ulcerations may require corrective surgery, because the underlying tissue may maintain the ulcer and the recovery of the immediate surrounding tissue may be slow.[45] Chronic radiation exposure (chronic radiodermatitis) can also lead to increased fibrosis and to ulceration.[42,45] Skin cancers may be evident after months or years.[42,45,49,54] They may result from either acute or chronic exposure, but are not generally associated with increased mortality.[7,8,45]

Radiation induces a bluish-brown pigmentation of the fingernails in persons of dark-skinned races.[39] The threshold dose has not been determined. Fingernail pigmentation was observed in the Marshall Islanders, who received an average estimated whole-body gamma-radiation dose of 61 rem. The bluish-brown pigment was slowly eliminated by normal fingernail growth over the first 6 months after irradiation.[39] Cracking or shedding of the nails may occasionally occur.[45]

The first report of epilation caused by X rays was written in 1896.[57] As a way to test the machine's ability to make a photograph of the skull (in preparation for locating a bullet in the head of a child who had been accidentally shot), the author exposed the head of a colleague to X radiation for 1 hour. The photograph did not

turn out, and 3 weeks later, the colleague developed a 2-inch bald spot on his scalp.[57]

Generally, epilation occurs about 2 weeks after irradiation with doses greater than 2-3 Gy.[10,42,54] This loss is temporary, with regrowth occurring in 2-6 months. The returning hair may be thinner, with either different pigmentation or loss of pigmentation. Permanent epilation occurs with doses greater than 6 Gy.[54] Epilation results from a combination of mitotic delay, interphase death, and reproductive death of the hair cell.

Cancer

Two months after their discovery, X rays were being used to treat cancer.[58,59] The earliest radiotherapy was performed in 1896 for breast carcinoma[58] and stomach tumors.[60,61] However, with the increasing use of radiotherapy came reports that radiation actually induces cancer.[51,58,59,62,63] One of the earliest radiation-induced cancers occurred in the laboratory of Thomas Edison, whose assistant died in 1904 from skin cancer contracted while working on the development of a fluorescent light using an X-ray tube.[58] By 1907, eleven mortalities were attributed to cancer induced by X radiation.[62] The first investigator to demonstrate that X radiation causes cancers in laboratory animals used a fractionated radiation schedule to induce spindle-cell carcinomas in rats.[64] Many early radiologists, researchers, and workers experienced chronic radiodermatitis, increased incidence of cancers, and other damage before the dangers of radiation were clarified and protective measures were initiated.[7,51,63] Now, the National Academy of Sciences considers cancer induction to be the most important somatic effect of low-dose ionizing radiation.[7]

Cancer Induction. Cancer development is thought to be a multistep process, in which the initial damage leads to a preneoplastic stage, followed by selection and proliferation of the neoplastic cell.[6-8,65-68] Chromosomal and enzymatic analyses indicate that all of the cancer cells of a tumor and its metastases are derivatives or clones of a single cell.[69-71] A neoplasm is characterized by unrestrained growth, irregular migration, transformation, and genetic diversity.[67]

The three stages in cancer formation are *initiation, promotion,* and *latency* (Figure 9-6).[7,65] During initiation, fixation of the somatic mutational event occurs, which leads to the development of a neoplasm. Damage can be initiated by various agents, including exposure to radiation or another environmental or chemical carcinogen.

During the promotion stage, the preneoplastic cell is stimulated to divide or is given preferential selection. A *promoter* is an agent that by itself does not cause cancer, but once the initiating carcinogenic event has occurred, it promotes or stimulates the cell containing the original damage.[65] The National Toxicology Program lists 148 chemical agents and groups known to be carcinogenic in

humans, including asbestos, benzene, vinyl chloride, nickel, soots, tars, formaldehyde, DDT, saccharin, and urethane.[72] Unlike most carcinogens, radiation may act both as an initiator by inducing somatic mutation, and as a promoter by stimulating cell division as a result of recovery and repair processes.[6,7] Some chemotherapeutic alkylating agents (including cyclophosphamide and nitrogen mustard) initiate biochemical damage similar to that caused by radiation, and are called *radiomimetic* agents. Like ionizing radiation, they are useful for chemotherapy but are also carcinogenic. Some hormones may act as promoters by stimulating the growth of target tissues.[7] For example, estrogen may function as a promoter of breast cancer, and thyroid-stimulating hormone (TSH) may act as a promoter of thyroid cancer. Conjugated and unconjugated estrogens have been identified as carcinogenic in human populations.[72]

Radiation may also affect latency, which is the third (and last) stage of cancer development. During latency, the transformed cell produces a number of different phenotypic clones through continued genetic diversity, although not all clones will be neoplastic.[65,67,68] Eventually, one phenotype acquires the selective advantage of evading the host's defense systems and metastasizing (Figure 9-6). The primary contributions of radiation in latency are the immunosuppression and alteration of biological mediators released in the surrounding tumor microenvironment.

Environmental and host factors have roles in cancer promotion.[6,7] The contribution of environmental agents can be estimated by comparing high and low cancer incidences in different populations of the world.[73] As many as 80% of cancer deaths in the United States may be linked to environmental factors that could have been avoided.[73] The incidence of lung cancer in males in the state of Connecticut in 1968-1972 was 325.8 cases per million males under 65 years old, compared to nine cases per million in rural Norway (Table 9-1).[73] Similar differences occur for the incidences of prostate cancer and myeloma in the populations of Connecticut and Miyagi, Japan. Environmental factors that may promote cancer are the use of tobacco, alcohol, and food additives; other dietary factors; sexual behavior; occupation; air pollution; industrial products; medicines and medical procedures; bacterial and viral infections; and geophysical factors.[73] Tumor registry studies have shown higher incidences of colon cancer in the United States than in Japan, while higher incidences of stomach cancer occur in Japan.[74] Japanese immigrants in the United States have a higher incidence of colon cancer than those living in Japan, indicating that environmental factors and dietary changes may influence its development. One environmental agent of increasing importance is the human immunodeficiency virus (HIV), implicated in the cause of acquired immune deficiency syndrome (AIDS).[75] This virus selectively attacks and destroys a subclass of T-cells (T-4 lymphocytes) that is responsible for monitoring the immunity of the spontaneously developing neoplastic cells. Impairment of the immune system may, therefore, promote cancer growth.

The differing incidences of cancer for males and females (Table 9-2) may be the result of hormonal, environmental, or behavioral factors. Leukemias and lung cancer are more prevalent in men. Their higher incidence of lung cancer may be due to the greater percentage of males who smoke. Thyroid cancers are more prevalent in women.[73] Genetic studies have shown that family tendencies for developing certain cancers are associated with several genetic syndromes, including xeroderma pigmentosum, ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome, Gardner's syndrome, and Li-Fraumeni's syndrome.[6-8,51,69,76] These diseases are associated with increased cellular mutation rates, sensitivity to environmental and chemical mutagens, and exposure to ionizing radiation. Chromosomal translocations are observed more frequently in cells from persons with these diseases, and specific defects in the repair of deoxyribonucleic acid (DNA) have been identified for most of these syndromes. These hereditary syndromes may increase susceptibility to cancer by providing the genetic diversity that is necessary for its development.[69,76]

Specific gene mutations and chromosomal aberrations are associated with particular cancers.[65-67, 69,77] Research in this area has been stimulated by the discovery in recent years of *oncogenes*, *proto-oncogenes,* and *antioricogmes.*[66,67,78,79]

Oncogenes are genes that induce the transformation of cells in culture when incorporated into the DNA of otherwise normal cells.[67] These genes have been found to have structural similarity to normally occurring genes that are present in nontransformed, noncancerous cells.[67,80] About forty different oncogenes have been identified.[79] Their functions are diverse; however, many of their gene products bind to DNA or promote cellular proliferation.[67,79,80]

The normally occurring counterpart of the oncogene is the proto-oncogene. Very few natural functions of the proto-oncogenes are known, although similarity exists between the v-sis oncogene and the gene coding for the platelet-derived growth factor-2 peptide.[80,81]

Most oncogenes were first isolated from avian leukemia retro-viruses, and later research identified oncogenic and normal counterparts in laboratory animals and in humans.[78] The viral oncogene is referred to as v-onc. One of the most commonly studied v-onc genes is v-myc.[67,79,80] Its homologous cellular gene (c-myc) is amplified in several different forms of cancer, including Burkitt's lymphoma in humans.[69,79,80,82] Another oncogene (ras) codes for a G-protein that regulates cell receptor activity by controlling adenyl cyclase activity.[83] Up to 40% of the surgically removed human colon cancers contain an activated ras oncogene.[84] Radiation-induced skin tumors in rats and mice have been found to have activated forms of the c-myc, k-ras, and ras oncogenes as well as amplification of the c-myc gene.[85-87] A mouse lymphoma induced by radiation was shown to have an activated c-k-ras oncogene that differed from the normal gene by a single point mutation, resulting in incorporation of aspartic acid instead of glycine into the corresponding protein.[87]

Oncogenic activation by itself is not necessarily a carcinogenic event because these genes have important normal cell functions.[67,69] They are thought to participate in initiating a neoplasm state by either quantitative or qualitative changes in their specified gene product as a result of amplification, mutation, or deregulation.[67,69,77] Some antioncogenes help repress cancer induction.[68,88] The deletion, inactivation, or presence of that gene in a homozygous recessive state may predispose or permit cancer development.[69,89] Hybridization experiments using normal cells and cancerous cells show that the cancerous actions of some oncogenes are repressed by the presence of the normal chromosome in the new hybrid.[69,90] An activated raf-oncogene has been implicated in the radioresistance of a human laryngeal cancer cell line[91] and also in radioresistant benign skin fibroblasts from a patient with Li-Fraumeni's syndrome.[76]

Radiation is known to induce chromosomal aberrations, and specific chromosomal aberrations are shown by many cancers. The most common translocations and trisomic conditions observed in human cancer involve chromosomes 1, 8, and 14.[69] The c-myc and c-mos genes are located on chromosome 8.[92,93] Translocation of chromosome 8 to 14 is present in 80% of patients with Burkitt's lymphoma and is associated with amplification of the c-myc gene.[77,92] A similar translocation occurs in 10%-20% of patients with acute T-cell leukemia.[77] The Philadelphia chromosome that is present in 90%-95% of patients with chronic myeloid leukemia is a translocation of a portion of chromo-some 9 to chromosome 22,[94-96] and it is thought to involve the c-abl proto-oncogene.[77,95-97] A transformation is thought to arise by random selection in the tumor cell due to its greater genetic diversity. Once present, the transformation provides a selective growth advantage that allows the cell possessing that modification to predominate.[65,66,69,98,99]

Models for Predicting Cancer Incidence. With few exceptions, radiation may induce cancer in any organ of the body.[7,8] Radiation-induced cancers cannot be distinguished from spontaneous cancers.[6,7,100] The possibility of radiation induction is based on a person's history of exposure to large doses, and is influenced by a number of variables, including total dose, dose rate, and radiation quality.[7,8] As with other somatic effects, genetic changes, and *in utero* effects, high-LET radiation and high dose rates have a greater probability of initiating or promoting cancer than does low-LET radiation. Most leukemias and cancers of the thyroid, breast, lung, liver, and bone are induced at higher rates by high-LET radiation, but the incidence is not large enough to allow accurate determination of the RBE in human populations. Low dose rates permit partial or complete cell repair of the radiation damage. In contrast, with high dose rates, the rate of cell damage may be faster than the repair rate, resulting in damage accumulation. Fractionation of the dose permits repair of a potential neoplasm and decreases the incidence of carcinogenesis for leukemia, but does not appear to be as important in reducing the incidence of breast and thyroid cancers. The latency and total risks for breast, lung, intestinal, stomach, and thyroid cancers vary with the age at exposure. In general, persons who are younger at the time of exposure are at increased risk for most cancers. For breast and thyroid cancers, persons younger than 20 years at the

time of exposure are more radiosensitive, whereas they are less radio-sensitive for stomach cancer and leukemia. The minimum latency periods are 2-3 years for leukemia and 5-40 years for solid tumors.

The probabilities of developing cancer as a result of exposure to high doses of either low- or high-LET radiation are fairly well established, but the risks of low-level exposure are not.[6-8] Insufficient data exist to accurately determine the risks to humans.[7,8,11,12] The risk for low-level exposure is extremely small and may be nonexistent.[7] Epidemiological analyses for determining the role of radiation exposure in carcinogenesis are made difficult by the small numbers of irradiated populations and the even smaller chance that a specific cancer resulting from a specific radiation exposure can be detected in a population.[7,8,11-13,101-103] Epidemiology is also clouded by the contributions of other carcinogens, differences in health factors, inappropriate control populations, and (in retrospective studies) possible death certificate inaccuracies, missing data in the records, and poor or biased memories.[11,102-104] The most recent estimates for the incidences of cancers resulting from 1 cGy of low-LET radiation are shown in Table 9-3.[11]

Within the limitations described above, the scientific community has attempted to derive risk estimates for low-level radiation exposures that may be used by legislative bodies to prescribe occupational and public safety standards. Four research models are used: *linear, linear-quadratic, quadratic,* and *pure quadratic with cell killing*.[6-8,13,101-103] Each model may exist with or without thresholds. Two of these models, linear and quadratic (nonlinear), are shown in Figure 9-7. A linear model is more likely to overestimate the incidence of cancer for lower doses. If the initial rate of increase is shallow for the lower doses, then a threshold essentially exists for the lower doses of a nonlinear model (Figure 9-7) because the incidence is extremely low in proportion to the dose. Different cancers may fit one model better than another. For some cancers, the confidence limits of the curve fit may not permit the selection of one model over another with any degree of accuracy. Figure 9-8 shows the degree of fit to the incidence of leukemia in the Nagasaki atomic-bomb survivors.[102] The data are best predicted by a linear-quadratic model,[6,11] although either model is applicable. The radiation-induced incidences of breast cancer and thyroid cancer are best described by linear models.[11] The cell-killing component of the pure-quadratic-with-cell-killing model refers to the fact that some incidence curves decrease at the higher radiation doses. Lower radiation doses increase the incidence of cancer cell induction, whereas the accumulated damage from higher doses is more likely to kill the cell, thus eliminating potential neoplasms.

HUMAN DATA BASE

Data from the human population on the effects of low-level radiation come from four sources (Table 9-4): atomic-bomb survivors, medical exposures, occupa-

tional exposures, and epidemiological comparisons of geographic areas containing high background radiation.[7,8]

The 92,231 survivors of the atomic detonations in Hiroshima and Nagasaki are being monitored by the Radiation Research Foundation for possible radiation-induced health effects.[105] Of the 24,000 deaths in this population through 1982, 6,720 were attributable to radiogenic and nonradiogenic cancers. The foundation is also following 27,000 children of the survivors who were conceived after the detonations to determine if genetic damage was induced in their parents and passed on to them.[106] Radiation doses received by a majority of the survivors were first determined in 1965,[107] and were recalculated in 1986 after more information on the explosions became available.[108] Earlier differences in the biological responses of the Hiroshima and Nagasaki populations were thought to be attributable to the larger neutron exposure and, hence, the greater RBE in the Hiroshima explosion,[7,8] however, reestimation of the radiation doses indicates less contribution from neutrons and a greater influence from gamma radiation in the Hiroshima bomb.[108] This necessitates revising the risk estimates for low-LET radiation exposure and may increase the potential risk estimates by 50%.[105]

The largest medically irradiated population for which dosimetry is available comprises the 14,111 patients in the United Kingdom who received spinal irradiation for treatment of ankylosing spondylitis.[8,13,109-111] Ankylosing spondylitis is a rheumatoid disease primarily affecting the spine and characterized by destruction of the cartilage and ossification of the vertebral joints. The patients received their radiation treatments sometime between 1935 and 1954. In the most recent study, they were monitored through 1970.[110] An increased incidence of leukemia has been observed in this population. Other medically irradiated groups with increased cancer incidence are children who received head radiation for treatment of tinea capitis,[112] and patients who received routine fluoroscopy examinations for postpartum mastitis[113] or during treatment of tuberculosis.[114,115]

The third category includes occupational groups with very low radiation doses (averaging less than 1 rem/year); the medical, scientific, and industrial professions; and victims of radiation accidents. In the early 1900s, workers in a number of occupations received large or chronic exposures to ionizing radiation because of inadequate safety standards and ignorance of its long-term biological effects. Three groups with a high incidence of radiation-induced cancer were the early radiologists, the radium-dial painters of the 1920s,[7,8] 1 and uranium miners.[116,117]

Leukemia

Leukemia is one of the most frequently observed radiation-induced cancers.[7,8,118] It accounts for one-sixth of the mortality associated with radiocarcinogenesis, with equal numbers of cancers of the lung, breast, and gastrointestinal tract.[7,8,11] Leukemia may be acute or chronic, and may take a lymphocytic or myeloid form.

With the exception of chronic lymphocytic leukemia, increases in all forms of leukemia have been detected in humans exposed to radiation and in irradiated laboratory animals.[6-8,51] More acute than chronic leukemias are induced, although the latencies are roughly equal.[51] Characteristic chromosomal aberrations induced by radiation have been identified in patients with either acute lymphocytic leukemia[119] or chronic myelogenous leukemia.[77,97] The most common aberration is the Philadelphia chromosome, found in approximately 95% of patients with chronic myelogenous leukemia.[76,94-96]

Leukemia first appeared in the atomic-bomb survivors 2-3 years after the nuclear detonations, and reached a peak incidence 10-15 years after irradiation.[7,8,51] The data for the Nagasaki atomic-bomb survivors best fit a linear-quadratic model (Figure 9-8), although the number of observations is so small that, statistically, either model fits well.[102] The average latency period for leukemia is thought to be 2-20 years.[7,8,11] The mean time from exposure to death was 6 years in the ankylosing spondylitis patients[109,110] and 13.7 years in the atomic-bomb casualties (Table 9-5).[51] The difference between the two groups may reflect the larger radiation dose (averaging 3.21 Gy) received by the bone marrow of the ankylosing spondylitis patients, compared to an average dose of 0.27 Gy in the atomic-bomb survivors. Table 9-5 shows the large numbers of observed leukemias in five irradiated populations compared to the predicted numbers. Between 1950 and 1972, sixty-three excess leukemia deaths occurred among the 92,000 survivors of the atomic bombs.[51,118,120] Results from a group of women in Scotland treated for metropathia hemorrhagica with pelvic X radiation are also shown in Table 9-5.[121] These patients received an average radiation dose of 1.34 Gy to the bone marrow, and have experienced increased incidences of leukemia and cancers at the site of irradiation (intestines, rectum, and uterus).

Thorotrast is a contrast medium that contains thorium-22 and decays by alpha emission (Table 9-5). It was used in diagnostic radiological procedures between 1928 and 1955.[7,8,51] An increased incidence of leukemia and liver cancer was observed in patients in whom thorium had concentrated in the liver and bone. The mean radiation dose to the bone marrow from Thorotrast ingestion was 3.5 Gy.[51] The estimated incidence of leukemia from 1 cGy of internal alpha radiation from Thorotrast is 32 persons per million, compared with 11.4 per million in the ankylosing spondylitis patients, who received 1 cGy of low-LET X radiation.[51] The alpha particle releases so much energy into a small area that most of the local tissue is destroyed before neoplasia occurs, thereby reducing the RBE for neoplasia. Although the risk of inducing cancer increases with an increasing dose, the accumulated damage results in the death of the cell before it can express its cancer potential. The RBE for leukemia induction by neutron radiation is estimated to be 1-25, according to data from the atomic-bomb survivors.[122]

The incidence of leukemia is influenced by age at the time of exposure (Figure 9-9). The younger the person at the time of exposure, the shorter the latency and the risk period for developing leukemia.[7,8] The incidence of leukemia decreases

with increasing age at the time of exposure; however, this individual is at increased risk for a greater period of time (Figure 9-9). Conversely, as the leukemia risk decreases, the risk of developing a solid tumor increases. For radiation doses of less than 0.2 Gy, there appears to be a threshold region in which increasing radiation doses carry slightly increased risks for leukemia induction.[102] This may simply be due to the sigmoid shape of the curve in the low-dose region, but the result is a quasi-threshold effect. Apparently no difference exists in the incidences of leukemia in females and males at any age or at any dose.[7,8,11]

Over 200,000 U.S. military and civilian personnel have been involved in the testing of nuclear weapons since 1945.[104] This number includes military personnel who were permitted to view a nuclear detonation from a safe distance. Later U.S. weapons testing occurred at the Nevada test site and at the Pacific Proving Ground in the Marshall Islands. The average doses received by the participants in those tests were 0.5 rem of gamma radiation and 0.005 rem of neutron radiation.[104] These doses were then and are now considered to be safe; Nuclear Regulatory Commission regulations permit persons in occupations with radiation exposures to receive 3 rem in any calendar quarter or 5 rem per year.[123] At the request of the Department of Defense, the National Research Council conducted a study of mortality among participants of nuclear weapons tests. The study included 46,000 of the approximately 200,000 test participants and, of these, 5,100 deaths occurred from all causes.[104] No increased incidence of leukemia was observed. Significantly fewer circulatory deaths occurred than expected (1,723 versus 2,541) as well as fewer cancer deaths (1,046 versus 1,243). The study concluded that "there is no consistent or statistically significant evidence for an increase in leukemia or other malignant disease in nuclear test participants."

However, a person who was present at the 1957 nuclear test shot (code-named SMOKY) developed leukemia 19 years later.[124] A follow-up study found a statistically significant increase of 8-10 cases of leukemia in the SMOKY test participants, compared with 3.5 leukemia cases expected in a general population of that size.[124,125] The increase could be due to chance alone because of the small population size or because of statistical fluctuation resulting from the *healthy worker effect.* The healthy worker effect states that is a small employed population, some change in mortality will occur if there is better health care, and this factor statistically sets that population apart from the general population. If mortality in one category decreases, then incidences in the other categories also shift. In-depth investigations by the Center for Disease Control and the National Research Council show that a healthy worker effect is present in the SMOKY test participants.[103,126] Few circulatory-related deaths occurred in the SMOKY participants (103 versus 139 expected in the general population) as well as fewer respiratory-related deaths (9 versus 17 expected).[126] Although the incidence of leukemia increased, the total incidence of cancers did not.

Thyroid Cancer

Thyroid cancer is also a concern for low-level exposure and late radiation effects (Figure 9-10), possibly accounting for 6%-12% of the mortality attributed to radiation-induced cancers.[7,8,11]

Radiation-induced thyroid cancer is 2.0-3.5 times more prevalent in women than in men (Figure 9-10 and Table 9-3).[7,8,11,127-132] Female atomic-bomb survivors had 3.5 times more thyroid cancer than male survivors,[11,129] and as much as 5 times more cancer in one clinical study.[128] The difference in thyroid tumor inductions in males and females is most likely due to hormonal influences on thyroid function.[8,133] Depressing TSH levels in irradiated rats by supplementing their diet with thyroxine reduces the incidence of thyroid cancer.[133] In the Marshall Islanders, the incidence of hypothyroidism is associated with elevated levels of TSH and closely matches the incidence of benign thyroid nodules.[50,134]

Variations also exist for ethnic groups. One study examined thyroid neoplasms in Jewish and gentile women who received radiotherapy during infancy for enlarged thymus glands.[128] The thyroid was in the exposure field during treatment and received a mean dose of 3.99 Gy. The risk of thyroid cancer in women of Jewish background was 163 per million women exposed to 1 cGy of low-LET radiation; in the gentile women studied, the risk was 48 per million.[120] Their risk was 16.5-fold greater than that for men in the same study. Persons of North African ancestory may also be at increased risk.[135]

A study on the atomic-bomb survivors,[129] two studies of 11,000 Israelis irradiated for tinea capitis,[127,135] and a study of patients treated by X-ray epilation for tinea capitis[112] indicate that the incidence of thyroid nodules is affected by the age at exposure. The risk is greater during the first two decades of life (Table 9-3).[11,127,135] Within this age range, children in the Israeli study who were younger than 6 years at the time of radiation treatment had a 1.6-2.3 times greater risk than their older counterparts.[135] The average dose received during treatment was less than 0.09 Gy.[136] Fourteen thyroid tumors occurred in 3,762 persons younger than 6 years at the time of exposure, compared with fifteen tumors per 7,080 persons 6-15 years old.[135] However, not all studies support an age effect.[59]

Thyroid neoplasms induced by radiation are the papillary (89%) and follicular (11 %) forms.[7] These forms are usually benign and slow growing, with an associated mortality rate of 5% (Figure 9-10).[7] In a 20-year follow-up of patients who received X radiation during infancy to shrink an enlarged thymus gland, 68% of the thyroid neoplasms were benign.[128] Of the surgically removed thyroid nodules that developed in the Marshall Islanders as a result of their fallout exposure, thirty-six out of forty-five (80%) were benign adenomas, and nine were malignant tumors consisting of seven occult papillary carcinomas and two papillary carcinomas.[50] Doses for these persons were 1-8 Gy. Malignant thyroid nodules tended to develop or to be detected earlier than the benign.[50,128,134] The latency

period for benign thyroid nodules is 5-34 years; for thyroid malignancies, 10-34 years.[7,11,128] In a follow-up investigation, an increase in thyroid neoplasms was observed in persons receiving X radiation in childhood for treatment of tinea capitis. The thyroid doses were 0.043-0.113 Gy with a mean of 0.09 Gy.[136] The dose response for thyroid cancer fits a linear pattern.[11] External radiation has a higher incidence of thyroid cancers than internal radiation.[137]

Irradiation of the thyroid may produce other responses, including hypothyroidism and thyroiditis. Hypothyroidism may occur in individuals receiving large sub-lethal radiation doses from external exposures. Threshold estimates for hypothyroidism in humans may vary by a factor of 25, from 2 Gy to 50 Gy, depending on whether the exposure source is external or internal.[10,137] Higher thresholds exist for internal irradiation (50 Gy), where the concentration of radioactive iodine by the thyroid may pose a problem.[137] Lower thresholds exist for children: 0.2 Gy for internal iodine-131 exposure and 1 Gy for external exposure. In the younger Marshall Island population exposed to 9 Gy, a high incidence of hypothyroidism occurred, characterized by elevated TSH levels. Above this dose, increasing incidence of hypofunction was associated with decreased carcinoma. Ten percent of persons with internal exposures of 200-300 Gy to the thyroid from radioactive iodine in fallout will develop symptoms of thyroiditis. At the upper end of that range estimate, thyroid ablation is likely.[137]

Breast Cancer

Breast cancer is the major concern for women exposed to low-level radiation because of its high incidence (Table 9-3) and 40%, mortality rate.[7,8,11,138] In the United States, one in eleven women will get breast cancer.[139] The incidence of mortality from breast cancer is almost nonexistent in men.[7,8,140,141] Because of their increased incidences of thyroid and breast cancer, women are also at greater risk of developing these cancers as a result of radiation.[7,8]

The risk of breast cancer associated with radiation exposure is age dependent (Table 9-3).[6,7,113-115,138,140,142] The absolute risk for women 10-19 years old at the time of exposure is 7.6 cases per million women per cGy of low-LET radiation; for persons over 40 years old, the risk is 0.8-1.3 cases per million.[11] In female adolescents, cancer does not become manifest until after puberty. Studies indicate increased incidence of breast cancer in atomic-bomb survivors who were younger than 10 years at the time of exposure.[140,143] Previous studies detected no increase in numbers of females of that age group.[144] Increases in breast cancer have been observed in women who received radiotherapy during infancy for treatment of enlarged thymus glands.[145]

The latency period for breast cancer is 5-40 years.[7,11,138,140,146] Women younger than 25 years have longer latencies than do older women, and in general, an increased incidence manifests itself in a woman's thirties and forties.[7,8,11,138,140,144] The mean latency period varies from 18 years in the atomic-bomb

survivors[51,144,146] to 27 years in one medical study.[114] Estrogen may promote breast cancer because a woman's age at exposure is associated with increased risk, and because few breast cancers occur until age 30.[7,51,140] This is supported by the fact that incidence of breast cancer does not increase in men following irradiation.[7,51,140,141] Several investigators have proposed that the actual period in which estrogen is present as a promoter is the important factor in determining cancer incidence and latency.[7,51,140] Women irradiated after menopause are less likely to incur radiation-induced breast cancer.[7,8,11,138,142] A decreased incidence of breast cancer was seen in women who received X-radiotherapy to the ovaries for metropathia hemorrhagica, although the incidence of radiation-induced leukemia did increase, as expected.[121] The radiotherapy induced an artificial menopause, with a corresponding decrease in estrogen production.

Breast cancer appears to fit a linear model.[7,11,51,146] If a threshold exists, it is in the range of 1 cGy, although a small increase in breast cancer occurred in atomic-bomb survivors who received exposures of less than 0.5 Gy.[7,51] The estimated dose of radiation required to double the naturally occurring incidence of breast cancer is 0.8 Gy.[138] A 1950-1977 study of 23,318 Canadian women who received less than 1 Gy from fluoroscopy during treatment of tuberculosis 20 years earlier showed no significant increase in risk of breast cancer,[138] but in another study, increases in breast cancer were observed in women who received multiple fluoroscopic examinations during tuberculosis treatment.[114] In another group of multiple fluoroscopy patients who received average doses of 0.66 Gy, no increase in cancer incidence was found.[147] These differences might be attributed to lower radiation doses and older age at exposure in the negative group.

Dose fractionation does not appear to reduce the incidence of breast cancer.[7,8,113-115] Damage in breast tissue tends to accumulate rather than to be repaired, so the risk from acute exposure (such as the atomic detonations) is the same as the risk from chronic exposure (such as small daily doses from fluoroscopy or treatment for postpartum mastitis) (Figure 9-11).[113] The data from medical studies and atomic-bomb survivors are very similar in their dose responses.[146]

Other Systemic Cancers

Cancers of the stomach, colon, liver, pancreas, salivary glands, lungs, and kidneys are also induced by radiation.[6-8,11] The incidences of these neoplasms fit a linear-quadratic response model. Like most solid tumors, they have a latency of 10-30 years, and no difference exists in the absolute risks for males and females.[11] With the exception of liver cancer, the radiation-associated risks depend on the age at exposure and increase with age.[6-8,11,51] The greatest risks are for induction of lung or stomach cancer in persons over age 50 at the time of exposure.[7,11] An association between radiation exposure and induction of brain tumors has been reported in two studies of children who received 1.4 Gy of X radiation as treatment for tinea capitis.[148,149] In the combined studies totaling 13,100 children, twenty-four tumors were observed, compared to three of 17,800 in the control population.

In the 1920s, workers who hand-painted the fluorescent dials on wristwatches with radium-based paint achieved the necessary fine detail by moistening the tip of the brush into a point with their tongues; in so doing, they ingested small amounts of the radium. Because radium is a bone-seeking element with a half-life of 1,600 years, these workers had a higher incidence of bone sarcomas. Increased incidences of breast cancer were also observed.[7,148,149]

Digestive System Cancers. Significant increases in cancers of the digestive tract, including the esophagus, stomach, and colon, have been observed in the atomic-bomb survivors[105] and in patients following therapeutic irradiation.[6-8,11] These cancers are ranked in order of descending radiation-induced cancer mortality as follows: *(a)* stomach, *(b)* colon, *(c)* pancreas, *(d)* esophagus, and *(e)* rectum.[11] This order reflects an averaging of the data; dose responses for rectal and pancreatic cancer are not significant in the atomic-bomb survivors.[105] Recent estimates by the National Institutes of Health indicate that stomach, colon, and esophageal cancers occur with greatest incidence in persons over 50 years old at the time of exposure (Table 9-3). The combined estimates in persons between 20 and 34 years old at the time of exposure for these three cancers is 1.068 excess cancers per million persons per year for each cGy of radiation. They will incur an increased risk for at least 20 years, beginning about 10 years after exposure, producing a total excess of 21 cancers. Although an estimate for 1 cGy was used, there is no statistical evidence demonstrating that these cancers can be induced by a dose this low. Environmental contributions from dietary and other sources may also influence the development of cancers of the digestive tract (Table 9-1).[73,74]

Tumors of the parotid gland have been observed 13-25 years after medical irradiation with doses as low as 0.9 Gy, and they may be either benign or malignant. In radiotherapy patients, large doses of radiation to the parotid and other salivary glands may result in atrophy, with subsequent difficulty in chewing food and swallowing due to loss of lubrication from saliva secretions.

Data on radiosensitivity of the liver are conflicting.[7,10,11] Several updated studies of the atomic-bomb survivors have failed to demonstrate a radiation dose-related increase in liver cancer.[105,120,152] Increased incidence of liver cancer is observed in patients treated with Thorotrast, although doubt exists about the origin of the disease in these patients.[7,51] There are three possibilities for cancer induction by Thorotrast: *(a)* alpha radiation exposure, *(b)* chemical toxicity from thorium dioxide, and *(c)* metal toxicity from several grams of thorium estimated to accumulate in the liver.[7,11] It is not likely that liver cancer is induced by alpha radiation from internal contamination with plutonium from fallout.[7] Estimates for liver cancer range from 5.6 to 15 deaths per million persons per cGy of external low-LET radiation.[7,11] Radiation hepatitis and cirrhosis of the liver may occur after large doses; may be acute, intermediate, or chronic; and may appear in some radiotherapy patients at 1-3 months after irradiation.[152,153] Sclerosis and blood-vessel narrowing appear to be primary factors in its development. Hepatitis has been observed following doses as low as 4 Gy, although most clinical cases

occur after 40-67 Gy.[153] Chronic radiation hepatitis is characterized by atrophy of the liver. Postnecrotic cirrhosis of the liver is two times greater in atomic-bomb survivors who received doses of less than 0.5 Gy, compared with the control population.[152]

Respiratory System Cancers. The induction of cancers may be affected by environmental factors, including occupational risks and personal habits, such as smoking (Figure 9-12).[7,11,73,85,154-156]

Workers in uranium mines and mills receive concentrated, high-LET alpha radiation from breathing uranium dust and concentrations of radon gas that seep into the mines from the surrounding rock.[7,51,120,121] Ore dust becomes trapped in the bronchi and alveoli and releases large amounts of radiation to the surrounding tissue, which leads to a higher incidence of lung cancer in this population.[16] In some areas, high radon concentrations in homes and buildings appear to contribute to lung cancer.[16]

In miners and atomic-bomb survivors, smoking has been shown to be an important contributing factor in lung cancer (Figure 9-12).[73,154-157] Risk estimates for radiation-induced lung cancer are four times higher for persons who smoke 1-10 cigarettes per day and twenty-four times higher for persons who smoke 40 cigarettes.[11] Increased cancer in smokers may result from the inhalation of volatile polonium-210, which is concentrated in the lungs and circulatory system.[155-157] Contributing factors are complicated, because the incidence of lung cancers induced by polonium-210 exposure can be enhanced in laboratory animals by the co-administration of saline.[158] Hamsters receiving 40 nCi of polonium-210 by intratracheal administration followed by saline had a 5% incidence of lung tumors, compared with 0% for hamsters receiving polonium-210 alone. In addition, cigarette smoke contains other carcinogens that may be important contributors to cancer development.[60,159]

Radiation pneumonitis will occur 1-7 months after irradiation in persons who survive large whole-body or upper-body exposures.[160] Studies of patients receiving single exposures for radiotherapy indicate that the threshold for this response is 7.5 Gy to the lung.[160] Since this dose is in the lethal range for the hematopoietic subsyndrome from whole-body exposure, the occurrence of pneumonitis will be limited, but it may be important as a late effect in patients receiving a bone-marrow transplant because of the larger radiation doses. A 5% incidence of radiation-induced pneumonitis is expected after a dose of 8.2 Gy, and a 50% incidence is expected at 9.3 Gy.[160] Characteristic symptoms include dyspnea, tachypnea, and coughing. Severe cases may result in death. Radiation pneumonitis is usually followed within 6-12 months by persistent pulmonary fibrosis.[161]

Reproductive System Cancers. A significant increase in malignant and benign tumors of the ovaries occurred in the atomic-bomb survivors between 1965 and

1980.[162] The latency period was 15 years, and a greater frequency was observed in women who were younger than 20 years at the time of exposure.

Cancers of Negligible Risk

Several types of cancer have a low or negligible risk of induction from radiation exposure. No increase in chronic lymphocytic leukemia has been observed to date in irradiated populations,[7] and increases in hairy cell leukemia are low or non-existent.[11] Cancers of the uterus, cervix, testis, mesentery, prostate, and mesothelium also have a low or nonexistent risk.[7,154] Some cancers are thought to be relatively insensitive to induction by radiation yet still have a small probability of occurrence, such as cancers of the larynx, nasal sinuses, parathyroid, nervous tissue, and connective tissue.[7,105]

In the most recent mortality study of the atomic-bomb survivors, the frequency of cancer of the rectum, gallbladder, pancreas, uterus, lymph glands, and nervous system was not statistically increased.[105] Cancers with a low probability of induction are not observed following low-level radiation because of the apparent long latencies.[7,105]

GENETIC EFFECTS

In 1927, radiation was conclusively shown to damage cells.[163] *Drosophila melanogaster* (fruit fly) sperm were irradiated, and radiation-induced increases were seen in *(a)* mutations leading to mortality and *(b)* mutations of characteristic morphological and phenotypic traits, such as wing shape and eye color. Since then, radiation-induced genetic damage has been consistently demonstrated in plant and animal species, leading to the conclusions that *(a)* radiation is a potent mutagenic agent, *(b)* most radiation-induced mutations are considered to be detrimental, and *(c)* radiation-induced genetic damage is thought to have no threshold, so even very small doses of radiation carry potential risk.[7,8,164-167] The natural incidence of genetic disorders is one in ten for live births and five in ten for spontaneous abortions. Background radiation (200 mrem per person per year) may account for up to 5% of the spontaneous genetic damage in the general population. Radiation causes genetic damage by either *gene mutations* or *chromosomal damage*.[7,8,164-169]

Gene Mutations

Gene mutations are alterations in a single gene locus, which is the smallest amount of genetic information that can code for a single protein. The gene is composed of DNA (Figure 9-13), which is made up of four bases: adenine, guanine, cytosine, and thymine. A group of three bases on a single strand of DNA represents a *codon*, coding for the insertion of one of twenty different amino acids into the protein to be synthesized. A change in one of the three bases within a

codon changes the blueprint for the amino acid to be incorporated into the protein at that position.

Radiation may cause point mutations, deletions, insertions, and inversions.[7,8,165,167] The mutation may occur in either the DNA sequence coding for the protein itself or in one of the regions regulating gene transcription. Mutations in the regulatory region of the gene may modify or shut off a transcription. Some oncogenes, such as the myc-c oncogene, may induce a precancerous state and increased cell proliferation by *(a)* mutation in the promotor region, or *(b)* a translocation that places the gene in a constant state of activation and transcription.[66,82,98] A point mutation occurs through a change in a single base within the gene (Figure 9-14). By changing one base, the codon is altered to represent a different amino acid and may affect the function of the protein. Sickle cell anemia, for example, is a disease resulting from a single point mutation. One form of the ras oncogene has been found to differ from the normal by a point mutation, and this change in one base now codes for a protein that transforms cells in culture to a neoplastic state.[98] A major concern for radiation genetics is the induction of a dominant gene carrying a trait that results in increased mortality or severe impairment[7,8,10,165,168,169] Examples of autosomal dominant genes are shown in Table 9-6, although many more exist.[8] As a random mutagenic agent, radiation may induce mutation in any gene. There are no radiation-specific mutations; radiation simply increases the incidence of those that occur naturally.[7,8] The examples in this section should not be regarded as those of radiation-specific mutations occurring after radiation exposure, but rather as particular classes of mutations (dominant or recessive). Of particular concern is the induction of genes that do not become expressed until after the individual has reached reproductive age.[7,8,165,168,169] An example of such a genetic disease occurring in the natural population is Huntington's chorea, a neurological degenerative disease that does not become symptomatic until individuals reach their twenties or thirties.

Recessive radiogenic gene mutations are of less concern since they require homozygosity in order to be expressed. Recessive genes are of more concern when they are located on the X chromosome. Since only one copy of the genes on the X chromosome exists in males, those genes are dominant in their expression. Hemophilia, for example, is a recessive trait on the X chromosome in the natural gene pool that may be expressed as a dominant condition in males (Table 9-6).

Chromosomal Damage

Radiation may also induce genetic damage by chromosomal changes.[7,8] The expression of a number of genes may be altered by damaging a portion of or a whole chromosome. Chromosomal changes may arise either as *chromosomal aberrations* or by *nondisjunction*, resulting in an unequal number of chromosomes.[7,8] Chromosomal aberrations are changes in the size, morphology, or number of chromosomes, and include dicentrics, acentrics, fragments, translocations, inversions, insertions, and deletions (Figure 9-15).[7,8,165,168,169] The

most common chromosomal damage induced by radiation is *reciprocal translocation*.[8] In this process, two different chromosomes experience double-stranded DNA breaks, and the two fragments rejoin to different chromosomes rather than those to which they were originally attached. By rejoining to a chromosome containing a centromere, the translocated piece may be transferred into the new gamete during division rather than be lost as an isolated fragment.

Chromosomal aberrations can be produced in both somatic and germ cells, and their frequency is proportional to the dose of radiation received.[170,171] Acentric and dicentric fragments are the most lethal because they may not properly separate at meiosis or mitosis and thus may halt those cellular processes. As a somatic mutation, the percentage of chromosomal aberrations in the lymphocytes of irradiated humans has been used to estimate the dose received. Such damage persisted in the lymphocytes of the atomic-bomb survivors 23 years after their exposure.[172]

The gain or loss of an entire chromosome through nondisjunction occurs less frequently and is more likely to result in mortality.[7,8] Mammalian studies have been unable to demonstrate increased incidence of trisomies in the offspring of irradiated animals.

Factors Affecting Mutation

A number of factors affect the ability of radiation to induce mutations, including rate of biological repair, dose rate, shielding, and number of exposures.[7,8,165,168,169,173] Several enzyme systems constantly monitor and repair the DNA, recognizing specific kinds of base damage and initiating repair.[174] During excision repair, for example, enzymes recognize the damaged part and split the DNA strand to remove it. The other strand then serves as a template to reincorporate the proper bases in the excised site, followed by action of a DNA ligase that reseals the strand. Breaks in the DNA strands may also be reconnected, although proper rejoining (if it occurs at all) becomes more difficult if a break has occurred in both DNA strands.[174,175] Other enzymes repair specific base damage, such as alkylations. Fractionation of the radiation dose can reduce the damage by allowing repair to occur between exposures. If the rate of damage exceeds the rate of repair, then the mutation rate will increase. Experiments in mice show that mutation rates do not further decrease at dose rates below 8 mGy/minute.[166] Dose rates in this range are about one-third as effective as high dose rates of gamma radiation in producing specific locus mutations in mice. High-LET radiations, such as neutrons, impart more energy per unit distance traveled through a biological material than do low-LET radiations. More energy deposited in the area of the DNA is more likely to produce more damage, increasing the likelihood of breaking both strands of the DNA.

Some DNA bases undergo spontaneous deamination. Deamination of cytosine produces uridine, which occurs in ribonucleic acid (RNA) but not in DNA. Unless

the deamination product is enzymatically corrected before replication, it can be mispaired, producing a base substitution in the newly replicated strand. Spontaneous deamination can be accelerated by increases in temperature.

Six genetic syndromes are known to be more sensitive to ultraviolet light or X-radiation damage to cells in culture, and they are associated with increased incidence of cancer.[7,8,69] These include xeroderma pigmentosum, Down's syndrome, ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome, and Cockayne's syndrome.[8] Most have associated defects in DNA-repair capability and increases in chromosomal aberrations. Age and gender are important secondary determinants for mutagenesis; for instance, studies show that the mother's age at the time of conception is an important factor in the incidence of Down's syndrome. The natural rate of chromosomal abnormalities is eight times higher in children whose mothers were 40 years old at the time of conception than in children whose mothers were 20 years old.[176] Paternal age at time of conception is also of concern, because the risk for a dominant gene mutation in the germ cells of men 30 years old and older is at least eleven times greater than in men who are younger than 30 years at the time of conception.[177]

Internalized radionuclides of hydrogen, carbon, and phosphorus may present special genetic damage, because these elements are the basic elements found in DNA.[178] The radionuclides may damage the DNA when they release their energy through beta decay and as they undergo transmutation, resulting in structural damage at the molecular site of incorporation.[7,178,179] Carbon-14 located in a sugar or base of the DNA decays to nitrogen-14. Tritium (hydrogen-3) decays to helium-3, and phosphorus-32 decays to sulfur-32. Transmutation of the phosphorous-32 in the sugar phosphate DNA chain can produce a strand break.
Plutonium-239, an alpha emitter, has induced genetic damage in mice following internalization.[7,8] Other alpha and beta emitters from internalized fallout will present similar problems. The RBE in mice following injection of plutonium-239 citrate ranges from four for specific locus mutations to fifty for translations.[7]

Radiation-Induced Damage in Humans

Evidence is lacking for radiation-induced genetic mutation in humans, although mutations of human cells in culture have been shown.[7,8] Based on current risk estimates, the expected increase of genetic damage in the atomic-bomb survivors is so low that it would not be detectable within the larger normal spontaneous incidence.[7,8,10] In screening twenty-eight different protein loci (498,000 loci tested) in the blood of 27,000 children of atomic-bomb survivors, only two children presented mutations that might be related to the radiation exposure of the parents.[106]

Early studies on the survivors' children examined whether radiation exposure caused an increase in sex-linked lethal genes that would result in increased prenatal death of males or alteration of the gender birth ratio.[180] Data did not

support that hypothesis. Twelve studies have examined a possible increase in the incidence of Down's syndrome as a result of maternal irradiation,[8,165] but only four of the studies showed statistical significance,[181-184] and the hypothesis has not received widespread acceptance. Irradiation of the human testes has been shown to produce an increase in the incidence of translocations,[185] although no additional chromosomal aberrations have been detected in children of the atomic-bomb survivors.[8,186]

Estimating Genetic Risks

The *genetically significant dose* (GSD) is the dose of ionizing radiation to the gonads that may result in increased incidence of genetic mutations in germ cells.[7,8] Estimation of the GSD takes into account the number of persons of reproductive age in a particular group in determining a collective dose. In the United States, the GSD from background and generated radiation sources is 122 mrem per person (Table 9-7).[7] The GSD from occupational exposure in the military service is less than 0.04 mrem per person, which is less than that received in a national research laboratory (< 0.2 mrem/year) or a nuclear power plant (< 0.15 mrem/year). Most occupational exposures are less than those received from consumer products over the same period.

Another method of estimating radiation-induced genetic damage is the calculation of the *doubling dose*, or radiation dose required to double the spontaneous mutation rate.[7,8] The spontaneous mutation rate in humans is 5×10^{-6} per locus, and $6.7\text{-}15.1 \times 10^{-4}$ per gamete for chromosomal anomalies.[7] The doubling dose is 0.5-2.5 Gy of low-LET gamma or X radiation, and 1 Gy is commonly used for calculation purposes.[8] The doubling dose for specific locus mutations in mice with low dose rates (< 8 mGy/minute) of low-LET gamma radiation is about 1.1 Gy.[185]

The effects of radiation exposure on the human population have been examined by several national and international scientific committees, including the National Academy of Sciences Committee on Biological Effects of Ionizing Radiation;[7] the United Nations Scientific Committee on Effects of Atomic Radiation;[8,51] and the International Commission on Radiological Protection (ICRP).[187] These groups arrived at similar estimates for the effects of low-level exposure to ionizing radiation (Table 9-8, Table 9-9).

The National Academy of Sciences estimates that for an exposure of 1 cGy to the present generation, there will be 5-65 additional genetic disorders per million births in the succeeding generation resulting from increases in autosomal dominant mutations and sex-linked dominant mutations. If a population is continually exposed to an increased radiation dose of 1 cGy for each generation, an equilibrium will be reached between the induction of new genetic disorders and the loss of the earlier induced disorders. In this equilibrium, an additional 60-1,100 genetic disorders would be expected in the population, with the majority

contributed by autosomal dominant and sex-linked recessive mutations and a large contribution from irregularly inherited genes. Irregularly inherited genes make up family tendencies for diseases and situations of incomplete dominance (where phenotypic expression is neither the recessive trait nor the dominant trait, but a blend of the two). Chromosomal damage and recessive mutations are thought to make minor contributions to the equilibrium rate. Chromosomal damage and loss are generally either lethal or selected out, while recessives are expressed only in the homozygous condition. The National Academy of Sciences does not provide a confidence interval or a geometric mean for its 60-1,100 range of additional genetic disorders in the next generation per million births.[7,10]

The ICRP estimates that for every million individuals receiving 1 cGy of radiation in the present generation, 125 additional cases of serious genetic disorders will occur over the next two generations.[187] Approximately half will come from dominant, sex-linked, and irregularly inherited mutations. Of the 125 cases, 89 will occur in the first generation. If a doubling dose method is used, then (assuming a doubling dose of 1 Gy) 1,500 autosomal dominant and gender-linked diseases per million live births would be observed in the first generation, and 10,000 (approximately the normal incidence) would be observed in succeeding generations exposed to 1 Gy at equilibrium. The total incidence of genetic disorders, one in ten live births, would not be reached in equilibrium with a 1-Gy doubling dose, since the doubling dose cannot approximate the irregularly inherited component.[8,10] Table 9-8 does not contain an estimated contribution for the irregularly inherited disorders in the first generation. The large variation within the equilibrium category is responsible for the large range (60-1,100) of total disorders expected in the equilibrium generation.

Using the doubling-dose method, the U.N. committee predicts that after exposure to 1 Gy, a total of 2,190 additional genetic disorders and an equilibrium of 14,900 will occur per million live births in the first generation after exposure (Table 9-9). Assuming a linear response, the U.N. committee estimates a mean of 22 disorders per million live births compared to the 5-65 disorders per million live births predicted by the National Academy of Sciences for a population exposed to 1 cGy. The U.N. committee extended its estimates to the detrimental effects of radiation exposure on the general population. The average dominant mutation in children of parents receiving a 1-Gy radiation dose would result in 25 years of impaired life, with death occurring 13 years prematurely. Overall, a 1-Gy exposure to parents would result in a total of 53,800 years of impaired life per million births from all causes of radiation-induced genetic damage, and a loss of 47,200 years of life in the succeeding generation. Through natural selection, the gene pool has the capacity to absorb large amounts of damage without destroying the population. A dose of 1 Gy to each generation would produce an equilibrium of 14,900 genetic disorders per million live births, compared to a normal incidence of one in ten. This is an increase of only 1.5%.

The immature human oocyte is thought to be only 44% as radiosensitive for mutation induction as the male spermatocyte.[7,8] The U.N. committee has estimated that most of the genetic damage induced by low-LET radiation will be unbalanced translocations, and that a 1-Gy low-LET exposure would induce 440-17,500 unbalanced translocations per million spermatogonia but only 0-5,250 in human oocytes (Table 9-10). These estimates were based on data for spermatocytes from rhesus monkeys, marmosets, and humans. Using the direct method, 1,000-2,000 dominant mutations per million births will be expected in the first generation following paternal irradiation of 1 Gy, but only 0-900 following maternal irradiation with the same dose.

RADIATION EFFECTS *IN UTERO*

The developing embryo is extremely sensitive to ionizing radiation, and the public has shown increased awareness and concern for exposure of the fetus to low-level radiation. Human and laboratory animal data indicate that doses as low as 0.05 or 0.1 Gy may induce effects.[7,51] Thresholds are thought to exist for the induction of *in utero* responses because most occur after damage to more than one cell.[7]

Stages of Development

The gestation period can be divided into three stages of embryo development: *preimplantation*, *major organogenesis*, and *fetal.* In humans, the preimplantation stage begins with the union of sperm and egg, and continues through day 9 when the zygote becomes embedded in the intrauterine wall. During this time, the two pronuclei fuse, cleave, and form the morula and blastula.

Major organogenesis begins on day 9-11 in humans[188,189] and continues through day 45.[180,189] The organ systems undergo differentiation and development. Neural cells are the first to differentiate, starting on day 17-20.[192,193] Neural development continues throughout the major organogenesis period and into the fetal period. The fetal stage covers weeks 7-38, or term.[191]

Four general responses may occur after radiation exposure *in utero,* depending on the stage of gestation at the time of exposure. These responses range from no detectable effect to prenatal death, neonatal death, or induction of congenital anomalies.[194]

Preimplantation

The embryo is extremely radiosensitive during the preimplantation stage, and radiation can cause increased prenatal death and reabsorption of the embryonic tissue.[188,194] In humans, reabsorption does not occur, but there is an increase in prenatal death. In animals, the incidence of prenatal death decreases as development proceeds into the major organogenesis stage, and it varies with the

dose and time of exposure.[7,51,188,194] During this period, the incidence of congenital anomalies is low but not absent. Surviving embryos show an all-or-none response that is essentially normal with no visible anomalies, even though radiation may have killed many cells.[188,194] During organogenesis, similar radiation doses might produce 100% incidence of a particular anomaly and probable growth retardation.[51,188,194]

Several factors, including repair capability,[188] undifferentiation, and a possible hypoxic state,[9] are thought to account for the decreased ability of radiation to induce anomalies during the preimplantation period. During the first few divisions, the cells are undifferentiated and lack predetermination for particular organ systems. If cell death were to occur following radiation exposure at this stage, the remaining cells could continue the embryonic development without gross malformation because they are still indeterminant. However, chromosomal damage at this point may be passed on to appear in later stages. When cells are no longer indeterminant, loss may lead to anomalies, growth retardation, or death. In mice, low incidences of exencephaly[195] and skeletal anomalies[196] have been observed following high-dose irradiation during preimplantation. At a critical period, 0.5 Gy may cause polydactyly.[197]

In laboratory animals, the incidence of prenatal death can vary with the dose of radiation and the time of exposure.[188,189,194] The most sensitive times of exposure in humans are at 12 hours after conception, when the two pronuclei fuse to the one-cell stage, and again at 30 and 60 hours, when the first two divisions occur.[197,198] At periods just preceding the cleavages, there would be insufficient time for repair of damage. In animals, 30% of the prenatal death at this time is because of radiation damage to the mother and a subsequent termination of pregnancy, rather than because of direct radiation damage to the embryo.[194]

Chromosomal aberrations from radiation exposure at the one-cell stage could result in the loss of a chromosome in subsequent divisions that would be uniform throughout the embryo.[7,51,199] Most chromosomal losses lead to prenatal death, although the loss of a sex chromosome in females may instead produce Turner's syndrome.[7,199] Such individuals are phenotypically female. Al-though this might indicate that a slightly higher proportion of phenotypic females will result from radiation exposure during this period, an altered gender ratio was not found in the children of the atomic-bomb survivors[180] or in laboratory mice irradiated during precleavage.[188] In mice, a dose of 1 Gy on day 0 (preimplantation) resulted in 50% prenatal death and produced loss of a sex chromosome in 4% of survivors. A prenatal mortality of 25% and a sex-chromosome loss in 0.5% of survivors occurred when the same dose was given 7 hours later.[199]

Major Organogenesis

Embryo malformation occurs most frequently with radiation exposure during the organogenesis stage, and the resulting incidences of abnormalities and prenatal

death will peak during this time.[7-9,51,194] However, the incidence of prenatal death decreases rapidly with increasing embryo development, and becomes equal to that of the control group when three-fourths of this stage has been completed.

The produced effects depend on the stage of development in which irradiation occurs, the dose, and the dose rate.[7-9,51,194] Most anomalies have a *critical period* during which the radiation exposure will result in the highest incidence of that anomaly (Figure 9-16).[188,190,194] Critical period is sometimes misinterpreted to mean that the particular organ tissue is in its most sensitive or major developmental period. This, however, may not necessarily be the case. Increased incidence during this time may be the result of indirect effects arising from damage to the adjacent tissue or from an inducer material of that organ.[51,194]

Each organ system is not at identical risk during the entire major organogenesis period because each organ is not developing at the same rate. Some organs may require the development of another organ or inducement before undergoing development themselves. Some anomalies may have more than one critical period. As a congenital anomaly in mice, cataract formation has three critical periods: 0-4 days, 8-9 days, and 14-17 days. These periods are due to the critical periods of several different systems that may in turn influence cataract formation. A slight but significant increased incidence may be observed with lower doses of radiation during the critical period.[190,194] A dose as low as 0.05 Gy may cause polydactyly,[197] skeletal malformation, decreased litter weight, and reduced tail length in mice.[200] Similar low doses have produced anomalies in the human,[201] monkey;[202] rabbit,[203] and rat.[204] *In utero* exposure to doses of less than 0.05 Gy from the Hiroshima atomic bomb resulted in an 11% increase in microcephaly.[7,204] Small continuous radiation exposures to rats from either X rays (1 cGy/day) or tritiated water (0.3-3.0 cGy/day) throughout their pregnancies produced decreases in brain weight.[7,205,206] Low doses of X radiation have also produced growth retardation[201] and behavioral defects.[207,208] Protracted low doses commonly affect the nervous system and the germ cells (ovaries and testes). The long, continuous development of the nervous system makes it sensitive to damage by even these low doses.[192,193,209-211] The range of a particular critical period may be extended by increasing the dose of radiation. Radiation does not increase the length of pregnancy in laboratory animals.[194] Fractionation of the radiation dose may produce either an increase or a decrease in the incidence of anomalies, depending on the time between exposures. If the critical period has a narrow time window, then fractionation over short periods of time may increase the damage by placing more radiation in the critical period and producing more mitotic death. Exposures at an early stage will increase the sensitivity to radiation exposure in a later critical period.

Variations in natural background radiation have not produced significant differences in the incidence of anomalies, although environmental factors may play a role in their induction.[7,51,212,213] The incidence of congenital malformations in mammals may be affected by seasonal differences, with greater sensitivity in

winter.[214,215] In the human, 70% of trisomy 18 (Edward's syndrome) and trisomy 13-15 (Patau's syndrome) live births are conceived in the winter.[216] In laboratory animals, anomalies such as those for the rear appendages and eyes have a greater incidence on the right side of the body than on the left.[197,216]

Anomalies may arise in several ways. Radiation may damage the primordial tissue of a particular organ or limb by direct or indirect damage to the chromosome or gene.[194] This in turn may result either in the failure to produce a functional gene product or in the production of an altered functional product. Radiation may cause nondisjunction during mitosis, resulting in a trisomic cell and a monosomic cell. Development would be affected to the extent that either cell predominates in an organ system.

Aberrations or other damage culminating in cell death could result in a reduction in the number of stem cells available for differentiation, which affects future organ systems. Growth reduction may result in the death of differentiated cells, leaving the embryo with a cell population too small to form the proper-sized organ.[217] A reduction in the size of one organ may cause changes in the surrounding tissues, such as microcephaly and mental retardation in humans irradiated *in utero*. The development of organs requires cell cooperation, mediated by chemical messengers such as hormones, organizers, and inducers. Destruction or damage to cells that contain organizers or chemical inducers may result in prenatal death or anomalies.[209] For example, the gray crescent material is an inducer that guides formation of the dorsal lip of the blastula, and eventually (through an area called the chorda-mesoderm) guides the development of the nervous system itself. Loss of the gray crescent or other inducer would modify or terminate subsequent development. Alterations in tissue contacts or areas of growth also may cause abnormal organ development.

The response of each organ to the induction of malformations is unique, based on dose, gestational age, type of radiation, RBE, oxygen tension, cell types undergoing differentiation, relationships to surrounding organs, and other factors.[7,51] Neutrons and beta particles are more effective at inducing congenital anomalies than is low-LET radiation. As an internal emitter, a beta particle released from tritiated water (or an alpha particle released from plutonium-239) would cause more damage because of its high LET and because there would be no maternal reduction of the dose. The high energy levels are released within the local area of the biological target. Neutrons have an RBE of 4.5 for inducing prenatal mortality in mice.[218] Animal studies in which either the mother or the embryo was shielded indicate that the induction of malformations is due mainly to direct damage to the embryo.[219-221] It is difficult to assign an overall risk estimate to the 119 different anomalies described in the literature because, like cancers, certain malformations are more inducible than others, and accounting for the variables becomes difficult.[7,51]

The Fetal Stage

The fetal stage is the final stage of development, lasting from the end of major organogenesis until birth. In mice, this covers days 14-20 of gestation;[188,194] in humans, days 45-266.[191] Radiation- induced prenatal death and anomalies are, for the most part, negligible during this stage. Anomalies of the nervous system and sense organs are the primary types that are inducible during the fetal stage because these systems are still developing. A radiation dose of 0.2-0.4 Gy given to rats on days 16, 18, or 22 of gestation caused delayed development, irregular arrangement, and loss of neurons in the brain cortex.[222] Irradiation on day 18 resulted in a 25% loss of neurons in the outer cortex, but no decrease in brain volume because there was an associated increase in glial cells. Much of the damage present during the fetal stage may not be manifested as behavior alteration or mental retardation until later in life. The incidence of neonatal-induced death also decreases with increased development during the fetal stage. The $LD_{50/30}$ for neonatal death given on day 10 of gestation to mouse embryos is about 1.15 Gy. By day 18 of gestation, the $LD_{50/30}$ is 6 Gy and rapidly approaches that of the adult animal.[217]

Stunting (retardation of growth) that is induced during this stage is a threshold phenomenon resulting from the killing of many cells. Since differentiated tissues (such as muscles and nerves) do not divide, cell death will lead to stunting that will still be evident in the adult. This has been demonstrated in children born soon after the atomic-bomb detonation who had received radiation exposures *in utero.*[223] Stunting has not been observed in laboratory animals that received less than 0.05 Gy or in humans exposed to doses of less than 0.3 Gy,[224] except in some of the Hiroshima atomic bomb survivors.[7,201] The sensitivity of some survivors who received lower radiation exposures may result from the contributions of neutron exposure and environmental factors.

Humans Irradiated *In Utero*

Two groups of humans who have been irradiated *in utero* are children of the atomic-bomb survivors and children whose mothers received medical irradiation (therapeutic or diagnostic) during pregnancy. The predominant effects observed in humans are microcephaly, mental retardation, and growth reduction (Figure 9-17).[7,51,193,201,225-229] Eye anomalies[227,228,230] and genital and skeletal abnormalities[211] are less frequently observed.

Microcephaly observed in children exposed *in utero* to the atomic-bomb radiation was proportional to the dose of radiation received by the mothers (Figure 9-18); even small doses carried increased incidence. Mothers with radiation sickness had higher fetal, neonatal, and infant mortalities.[231] Fetal mortality was highest in the first two trimesters, and neonatal and infant mortalities were highest in mothers who developed radiation sickness as a result of radiation exposure during the last two trimesters. In Nagasaki, four of sixteen surviving infants who *in utero* were

close to the epicenter of the explosion had speech impairments. In another study of 153 of these children, 33 had a head circumference two standard deviations below average. Mental and growth retardations were also associated with the increased incidence of microcephaly,[232-234] and they remained evident in these survivors as adults.[223,234] The highest incidence of microcephaly in Hiroshima occurred with radiation exposure in weeks 6-11 of gestation.[201] No incidence of microcephaly was observed during the first week of gestation (the preimplantation period) and was negligible for exposure after the 17th week. In the Nagasaki data, microcephaly did not occur with doses below 2 Gy.

Similar observations on radiation effects *in utero* have been reported after medical irradiation.[227-229] Twenty of twenty-eight children irradiated *in utero* as a result of pelvic radium or X-ray therapy to the mother were mentally retarded, and sixteen were also microcephalic.[228] Other deformities, including abnormal appendages, hydrocephaly, spina bifida, or blindness were found in eight of the children, and some also had language deficiencies. One child received a fractionated dose totaling 6.8 Gy in weeks 19, 22, and 27 of gestation and did not develop any obvious congenital anomalies or mental retardation.[235]

Increased incidence of eye anomalies has been observed following irradiation *in utero*.[227,230] In a review of twenty-six case histories, three primary eye anomalies were identified.[227] Three of twelve persons irradiated in weeks 3-8 developed cataracts; of fifteen irradiated in weeks 3-11, six had pigmentary degeneration of the retina and thirteen had microphthalmia. In the same patients, twenty-one were microcephalic; all had received radiation exposure some time in weeks 3-20, and most had been irradiated in weeks 3-11. Another study of 1,000 children exposed *in utero* showed no increase in nervous or eye anomalies but did show increased incidence of hemangioma (fifty-six versus thirty-seven in controls).[236]

Although each occurrence should be evaluated individually, the prevailing scientific opinion is that there are thresholds for the induction of congenital anomalies. Doses in the range of 0.10-0.15 Gy are thought to carry negligible risk.[7-9,51,225,226] Denmark's medical profession automatically recommends therapeutic abortion for any fetus exposed to 10 rem or more of radiation.[190] At one time, radiation was widely used to induce therapeutic abortion in cases in which surgery was deemed inadvisable. The standard treatment involved 3.6-5.1 Gy given over 2 days,[237,238] which was effective in 93% of cases.[237] Abortion usually occurred about 1 month after radiation treatment, in some cases inducing live birth.[237]

Increased Incidence of Cancer with *In Utero* Exposure

Increased incidence of leukemia and solid cancers may occur in children who received *in utero* exposure from diagnostic X-irradiation.[7,9,51,239-243] This observation was first reported in 1956 in a retrospective study of childhood cancer in Great Britain.[244] It has been confirmed by a similar study of 1.4 million children

born in the northeastern United States,[243] but was not observed in the atomic-bomb survivors.[7,51] The lack of increased frequency in the bomb survivors has been attributed to the smaller sample size, where only one or two extra cases of childhood leukemia might be expected on the basis of the other studies.[9] Most of the animal studies do not demonstrate elevated rates of neoplasms following *in utero* exposure.[51] Criticisms of these studies are based on objections that as-yet-undetermined factors may have affected the results. One postulate is that the mothers of children who developed cancer may have had complicated pregnancies requiring X-ray examination, and that the cause for the examination (and not the examination itself) was associated with the increased frequency. One study pointed out that a primary reason for prenatal X-ray examinations was to confirm a diagnosis of twins.[9] The incidence of childhood cancers in twins irradiated *in utero* was higher than in twins not irradiated *in utero*.

The human data have been evaluated by several scientific bodies, including the National Academy of Sciences[7] and the United Nations.[51] These organizations have subsequently derived risk estimates for carcinogenesis that results from *in utero* irradiation. Neoplasms were three times more frequent for *in utero* exposures occurring during the first trimester than in the second or third trimesters.[7,242] The peak incidence of childhood leukemia occurred between ages 2 and 4 and was higher in males.[240] The higher risk for developing one of the leukemias continues through the 10th year of life. Children may be at increased risk for developing solid tumors for at least 14 years,[7,9] many of which will be neoplasms of the nervous system.[51] All estimates of childhood cancer induced by radiation exposure *in utero* are based on the earlier mortality data and do not reflect the advances in modern treatment. In studies performed in the late 1940s and early 1950s, leukemia was a rapid, always-fatal disease with a 3-year survival rate of 2%.[73] By the early 1970s, 3-year survival rates were 20%, and today's cure rates are 40%-60%.[73] By today's standards, the estimates are likely to over-estimate the present mortality risks, because mortality is a different end point from incidence. Current estimates predict two to three leukemia deaths for each 10,000 children receiving 1 Gy of low-LET radiation *in utero.* Solid tumors will account for an additional 2.0-2.8 deaths in the same 10,000 children. The combined increased mortality from childhood cancer as a result of *in utero* exposure is 4.0-5.8 per 10,000 children per Gy. The natural total risk of mortality from malignancy through age 10 is one in 1,200. If an average chest X ray delivers 250 mGy to the fetus, the probability of that fetus developing a fatal cancer during childhood is one in a million. The NCRP recommends that fetal exposure be limited to 0.5 mSv (0.05 rem) per total gestation period or 0.05 Sv/month.[244] The increased risk for mortality in children receiving the limit of 0.05 Sv/month in a single exposure would be two to three per 100,000 children.

RELATIVE BIOLOGICAL EFFECTIVENESS OF NEUTRONS

Some doubt exists regarding the RBE of neutrons and other high-LET radiation for producing biological effects at low dose rates and doses. In general, high-LET radiation is more effective in producing biological damage. The biological effects observed in the atomic-bomb survivors are, for the most part, in agreement with human data from medical exposures. The RBE of neutrons for leukemia and breast cancer appears to be 1 in persons receiving acute or very rapid exposures.[122] As previously mentioned, the RBE of high-LET radiation increases with decreasing dose rate, because the effectiveness of low-LET gamma or X radiation decreases with decreasing dose rate. At low dose rates, the RBE for neutrons may range from 3 to 200 for tumor induction, from 10 to 45 for genetic end points, and from 25 to 200 for lens opacification.[244] These ranges are based on laboratory animal studies because no human populations have been exposed to pure neutron radiation.

REGULATORY GUIDES FOR EXPOSURE

Based on the scientific evidence, the United States government (through the Environmental Protection Agency and the Nuclear Regulatory Commission) has set regulatory guides for the occupational exposure of workers and for the general public.[123] The permissible concentrations for the occupational exposure to radiation workers (Table 9-11) are ten times higher than exposure levels for the general public. It is thought that the presumed detrimental effects on health from exposures at these limits are negligible. Scientific bodies continually reevaluate these risk estimates as additional information becomes available on radiation effects in human populations.

Modification of normal protection standards may be required in civil defense and military operations. Two limits for radiation exposure are recommended by NCRP for occupational radiation workers and for rescue personnel during radiation emer-gencies.[245,246] The first limit is a one-time whole-body exposure of 250 mSv, equivalent to a dose of 0.25 Gy of low-LET radiation.[246] This limit was later reduced to 100 mSv (0.1 Gy).[244] Doses of 100-250 mSv are generally asymptomatic, do not require medical treatment, and would result in three additional radiation-induced cancer mortalities over the lifetime of a battalion-sized group of 1,000 men.[7] The normal cancer incidence for this group is 250 cancers, with 200 cancer-related mortalities. It is unlikely that other somatic effects would be observed in this group. The earlier acute-exposure dose limit of 250 mSv (25 rem) is also the lower dose range estimate for inducing long-term fatigue in 10% of the individuals. Long-term fatigue occurs with doses of 250-650 mSv, with 50% incidence after a 150-mSv radiation dose received in 1 day.[10] For acute exposure in a single day, doses higher than 250 mSv may result in increased incidence of fatigue that may impair performance and alertness.

The second health limit for an acute exposure is a one-time exposure of 1 Gy of low-LET radiation in situations requiring lifesaving actions.[246] It also states that persons receiving doses greater than 1 Gy should understand the risks for somatic injury.[244] A dose of 1 Gy approaches the lower threshold limits for initiating the prodromal symptoms of nausea and vomiting and for hematological depression. At this dose level, approximately twelve extra cancer deaths would occur in a battalion-sized group of 1,000 men over their lifetimes. Minor visual opacities may occur in some of them. Both limits, 0.25 Gy (250 mSv) and 1 Gy (1 Sv), would result in temporary aspermia.[246] Lower doses of 0.01-0.02 Gy would result in 0.12-0.24 additional cancer deaths in the same battalion, assuming that no threshold for cancer exists.

The NCRP established a penalty table (Table 9-12) for making health-risk judgments in situations involving the exchange of nuclear weapons.[54] Based on the information for protracted exposures, no medical care should be required for low-LET radiation doses up to 1.5 Gy received over 1 week, or 2.0 Gy received over 1 month, or 3 Gy received over 4 months. For daily exposure of personnel over these same periods, the acceptable dose rates would be 0.21, 0.066, and 0.025 Gy/day, respectively. Animal studies have shown that the threshold dose is 0.05 Gy/day on a continuous basis, above which the stem cells are unable to compete with cell loss through maturation and depletion.[51] The immediate health concern is not cancer induction, although increased incidence will occur. Some persons exceeding these doses will require medical care, and some (5 % or greater) may die from the hematopoietic subsyndrome.

It is sometimes difficult for the public to place radiation risks in the proper perspective, perhaps because of their association with nuclear weapons, the documented effects from exposure, and the perception that radiation cannot be seen or controlled. Four-tenths of a minute of life are lost for each mile driven in a car due to the risk of a fatal accident, and the average smoker loses 10 minutes of life for each cigarette smoked. In comparison, an estimated average of 1.5 minutes of life are lost for each 0.0015-mSv (1.5-mrem) exposure to ionizing radiation.[245] It is expected that doubling the natural background radiation would result in an average loss of 8 days of life from the increased risk of cancer. The average coffee drinker may lose 6 days because of the increased risk of bladder cancer, and the average unmarried male may lose 9.6 years from his lifespan. For military personnel, the average loss of lifespan from a tour of duty in Vietnam was 1.1 years.[245]

The NCRP has defined a dose of 0.01 mSv per year, equivalent to 10 Gy or 1 mrad of low-LET radiation, as the negligible individual risk level.[244] This implies that almost every dose of radiation carries potential risk. In some cases, the risk is extremely small and difficult to identify, as illustrated by the comparison to smoking one cigarette. The goal is to keep exposures as low as is reasonably achievable in daily life and in emergency situations.

SUMMARY

The late effects of ionizing radiation can be divided into three major groups: somatic, genetic, and teratogenic effects. Somatic damage ranges from fibrosis and necrosis of individual organs to cataracts, epilation, and cancer.

Most somatic effects require high-threshold doses of radiation; cancer is the main health concern after exposure to low-level radiation. The three most common radiation-induced malignancies are leukemia, breast cancer, and thyroid cancer. The latency periods for the detection of cancer after radiation exposure range from 2 years for leukemia to 30-40 years for some solid tumors.

Mathematical models predicting cancer risks based on observations from high radiation exposures imply that 120-180 additional cancer deaths will occur for every million persons receiving 1 cGy of radiation. This estimate range includes the incidence of all cancers and presumes that no thresholds for induction exist. Some evidence indicates that thresholds for radiation-induced cancer do exist, ranging from 0.01 Gy for breast cancer to 0.2 Gy for leukemia.

Genetic effects are the second category of low-level or late effects of radiation. It is estimated that 5-65 additional genetic disorders will occur in the next generation for every million persons receiving 0.01 Gy of gamma or low-LET radiation. These disorders will be mainly autosomal dominant and gender-linked disorders. If each succeeding generation were to receive an additional 0.01 Gy of radiation, equilibrium would be reached in the gene pool, and an average increase of 60-1,100 genetic disorders per million persons would be observed in the population. This would result in a 1.5% increase in the overall incidence of genetic disorders. The normal incidence of genetic disorders in the population is one in ten.

The third category of late radiation damage is the teratogenic effects. The primary somatic effects seen in humans exposed *in utero* are microcephaly, mental retardation, and growth retardation. These effects have been observed with an increased incidence in the atomic-bomb survivors exposed *in utero* to doses of less than 0.10 Gy, although a neutron component may have enhanced the radiation effectiveness. In general, thresholds exist for the induction of birth defects by radiation, and effects below 0.10 Gy are negligible. The normal incidence of birth defects is one in ten live births. One concern for low-level exposure to ionizing radiation *in utero* is the increased incidence of cancer in childhood. An estimated twenty-five additional cancer deaths are predicted for every million children receiving 1 cGy of radiation *in utero.*

REFERENCES

1. Bacg, Z. M., and Alexander, P. 1966. *Fundamentals of radiobiology*. 2d ed., 45-62, 122-156. Oxford: Pergamon Press.

2. Snyder, S. L. 1977. Radiation-induced alterations in serum and splenic lysosomal hydrolases of the rat. *Radiat. Res*. 69: 306-316.

3. Donlon, M. A., and Walden, T. L., Jr. 1988. The release of biological mediators in response to acute radiation injury. *Comments on Toxicology* 2: 205-216.

4. Young, R. W. 1987. Acute radiation syndrome. In *Military Radiobiology,* edited by J. J. Conklin and R. I. Walker, 165-190. New York: Academic Press.

5. Glasstone, S. 1964. *The effects of nuclear weapons.* Rev. ed. Washington, DC: United States Atomic Energy Commission.

6. Upton, A. C. 1987. Cancer induction and non-stochastic effects. *Br. J. Radiol.* 60: 1-16.

7. Committee on the Biological Effects of Ionizing Radiation. 1980. *The effects on populations of exposure to low levels of ionizing radiation.* Washington, DC: National Academy Press.

8. United Nations Scientific Committee on the Effects of Atomic Radiation. 1982. *Ionizing radiation: Sources and biological effects.* New York: United Nations, New York.

9. Mole, R. H. 1987. Irradiation of the embryo and fetus. *Br. J. Radiol.* 60: 17-31.

10. Nuclear Regulatory Commission. 1985. *Health effects model for nuclear power plant accident consequences analysis* [U.S. Nuclear Regulatory Commission Contractor Report NUREG/CR-4214 (Sandia No. SAND85-7185)]. Washington, DC: U.S. Government Printing Office.

11. National Institutes of Health. 1985. *Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables* [NIH Publication No. 85-2748]. Washington, DC: Department of Health and Human Services.

12. Upton, A. C. 1982. The biological effects of low-level ionizing radiation. *Sci. Am.* 246: 41-49.

13. Webster, E. W. 1981. On the question of cancer induction by small X-ray doses. *Am. J. Radiol.* 137: 647-666.

14. Auxier, J. A., and Dickson, H. W. 1983. Guest editorial: Concern over recent use of the ALARA philosophy. *Health Phys.* 44: 595-600.

15. National Council on Radiation Protection and Measurements. 1977. *Radiation exposure from consumer products and miscellaneous sources* [NCRP Report No. 56]. Washington, DC: National Council on Radiation Protection and Measurements.

16. Harley, J. H. 1981. Radioactive emissions and radon. *Bull. NY Acad. Med.* 57: 883-896.

17. Upton, A. C.; Christenberry, K. W.; Melville, G. S.; Furth, J.; and Hurst, G. S. 1956. The relative biological effectiveness of neutrons, X-rays, and gamma rays for the production of lens opacities: Observations on mice, rats, guinea pigs, and rabbits. *Radiology* 67: 686-696.

18. Burch, P. R., and Chesters, M. S. 1985. Natural and radiation-induced cataracts in man and mouse, and natural macular degeneration in man: Proposed mechanisms. *Phys. Med. Biol.* 30: 879-896.

19. Toda, S.; Hosokawa, Y.; Choshi, K.; Nakano, A.; and Takahashi, M. 1964. Occular changes in A-bomb survivors exposed during infancy. *Folia Ophthalmol. Jap.* 15: 96-103.

20. Hirose, K. 1956. Occular lesions development after exposure to atomic bomb in Nagasaki city. In *Research in the effects and influences of the nuclear bomb test explosions,* compiled by the Committee for Compilation of Report on Research in the Effects of Radioactivity, 1655. Ueno, Japan: Japan Society for the Promotion of Science.

21. Messerschmidt, O. 1979. *Medical procedures in a nuclear disaster: Pathogenesis and therapy for nuclear-weapons injuries,* 187-190. Munich: Verlag Karl Theimig.

22. Otake, M., and Schull, W. J. 1982. The relationship of gamma and neutron radiation to posterior lenticular opacities among atomic bomb survivors in Hiroshima and Nagasaki. *Radiat. Res.* 92: 574-595.

23. Ham, W. T., Jr. 1953. Radiation cataract. *Arch. Ophthalmol.* 50: 618-643.

24. International Commission on Radiological Protection. 1984. Non-stochastic effects of ionizing radiation. In vol. 14, *Ann. ICRP* [ICRP Publication 41]. Oxford: Pergamon Press.

25. Ash, P. 1980. The influence of radiation on fertility in man. *Br. J. Radiol.* 53: 271-278.

26. Rowley, M. J.; Leach, D. R.; Warner, G. A.; and Heller. C. G. 1974. Effect of graded doses of ionizing radiation on the human testis. *Radiat. Res.* 59: 665-678.

27. Sandeman, T. F. 1966. The effects of X-irradiation on male human fertility. *Br. J. Radiol.* 39: 901-907.

28. Clifton, D. K., and Bremmer, W. J. 1983. The effect of testicular X-irradiation on spermatogenesis in man: A comparison with the mouse. *J. Androl.* 4: 387-392.

29. Carr, B. R., and Wilson, J. D. 1983. Disorders of the ovary and female reproductive tract. In *Harrison's Principles of Internal Medicine*, 10th ed., edited by P. G. Petersdorf, R. D. Adams, E. Braunwald, K. J. Isselbacher, J. B. Martin, and J. D. Wilson, 700-720. New York: McGraw-Hill.

30. Kaplan, I. I. 1959. Genetic effects in children and grandchildren of women treated for infertility and sterility by Roentgen therapy. Report of a study of thirty-three years. *Radiology* 72: 518-521.

31. Roentgen, W. C. 1895. Uber eine neue Art von Strahlen. *Sitzunsb. d. phys.-med. Gesellsch. zu Wurzb.* : 132-141.

32. Malkinson, F. D., and Keane, J. T. 1981. Radiobiology of the skin: Review of some effects on epidermis and hair. *J. Invest. Dermatol.* 77: 133-138.

33. Marcuse, W. 1896. Nactrag zu dem Fall von Dermatitis und Alopecie nach Durchleuchtungsversuchen mit Roentgenstrahlen. *Deut. med. Wochschr*. 22: 681-686.

34. Freund, L. 1897. Ein mit Roentgen-Strahlen behandelter Fall von Naevus pigmentosus piliferus. *Wien. Med. Wochschr*. 47: 428-434.

35. Hall-Edwards, J. 1904. On chronic X-ray dermatitis. *Br. J. Med.* 2: 993-995.

36. Harris, L. H. 1906. Treatment of chronic X-ray dermatitis. *Br. J. Med.* 2: 695.

37. Drury, H. C. 1896. Dermatitis caused by Roentgen X-rays. *Br. J. Med.* 2: 1377.

38. Mutscheller, A. 1925. Physical standards of protection against Roentgen-ray dangers. *Am. J. of Roentgenol. and Radium Ther.* 13: 65-70.

39. Cronkite, E. P.; Bond, V. P.; Conard, R. A.; Durham, C. L.; Farr, R. S.; Schulman, N. R.; Sondhaus, C. A.; Cohn, S. H.; Hechter, H. H.; Sharp, R.; Alpen,

E. L.; Browning, L. E.; Wood, D. A.; Rinehart, R. W.; Cong, J. K.; Robertson, J. S.; and Milne, W.L. 1956. *Some effects of ionizing radiation on human beings: A report on the Marshallese and Americans accidentally exposed to radiation fallout and a discussion of radiation injury in the human being* [U.S. Atomic Energy Commission Publication AEC-TID 5385]. Washington, DC: U.S. Government Printing Office.

40. Arlett, C., and Harcourt, S. 1980. Survey of radiosensitivity in a variety of human cell strains. *Cancer Res.* 40: 926-932.

41. Charles, M. W. 1986. Recent developments in the dosimetry of superficial tissues, I.1. *Br. J. Radiol.* (Suppl.) 19: 1-7.

42. Archambeau, J. O. 1987. Relative sensitivity of the integumentary system: Dose response of the epidermal, microvasculature, and dermal populations. *Adv. Radiat. Biol.* 12: 147-204.

43. Ernst, K., and Ehring, F. 1986. Unavoidable sequelae and accidental damage to the skin following irradiation. *Br. J. Radiol.* (Suppl.) 19: 15-18.

44. Dutreix, J. 1986. Human skin: Early and late reactions in relation to dose and its time distribution, II.1. *Br. J. Radial*. (Suppl.) 19: 22-27.

45. Malkinson, F. D., and Wiskemann. A. 1987. Some principles of radiobiology and the effects of ionizing radiation on the skin. In *Dermatology in General Medicine.* 3d ed., 1431-1440. New York: McGraw-Hill.

46. Trott, K.-R. 1986. What can the experience of radiation therapy teach us about accidents? *Br. j. Radiol.* (Suppl.) 19: 28-30.

47. Kalz, F. 1941. Theoretical considerations and clinical use of Grenz rays in dermatology. *Arch. Dermat. Syph.* 43: 447-472.

48. Stieve, F.-E. 1986. Experiences with accidents and consequences for treatment. *Br. J. Radiol.* (Suppl.) 19: 18-21.

49. Moritz, A. R., and Henriques, F. W., Jr. 1952. Effect of beta rays on the skin as a function of the energy, intensity and duration of radiation. II. Animal experiments. *Lab. Invest.* 1: 167-185.

50. Conard, R. A. 1984. Late radiation effects in Marshall Islanders exposed to fallout 28 years ago. In *Radiation Carcinogenesis: Epidemiology and Biological Significance,* edited by J. D. Boice and J. F. Fraumeni, 57-71. New York: Raven Press.

51. United Nations Scientific Committee on the Effects of Atomic Radiation. 1977. *Sources and effects of ionizing radiation*. New York: United Nations.

52. Snyder, D. S. 1976. Effect of topical indomethacin on UVR-induced redness and PGE levels in sunburned guinea pig skin. *Prostaglandins* 11: 631-643.

53. Lushbaugh, C.C.; Fry, S. A.; Ricks, R. C.; Hubner, K. F.; and Burr, W. W. 1986. Historical update of past and recent skin damage radiation accidents. *Br. J. Radiol.* (Suppl.) 19: 7-12.

54. National Council on Radiation Protection and Measurements. 1974. *Radiological factors affecting decision-making in a nuclear attack* [NCRP Report 42]. Washington, DC: National Council on Radiation Protection and Measurements.

55. Potten, C. S. 1986. Biological dosimetry of local radiation accidents of skin: Possible cytological and biochemical methods. *Br. J. Radiol.* (Suppl.) 19: 82-85.

56. Ruben, P., and Cassaret, G. W. 1968. *Clinical radiation pathology.* Philadelphia: Saunders.

57. Daniel, J. 1896. The X-rays. *Science* 3: 562-563.

58. Brown, P. 1936. *American martyrs to science through the Roentgen rays*, 6-13, 32-42. Springfield, IL: Charles C. Thomas.

59. Upton, A. C. 1964. Cancer research 1964: Thoughts on the contributions of radiobiology. *Cancer Res.* 24: 1860-1868.

60. Grubbe, E. H. 1902. X-rays in the treatment of cancer and other malignant diseases. *Medical Record* 62: 692-695.

61. Despeignes, V. 1896. Nouvelle observation de cancer traite par les rayons de Roentgen. *Lyon Med.* 83: 550.

62. Porter, C. A., and White, C. J. 1907. Multiple carcinomata following chronic X-ray dermatitis. *Ann. Surg*. 46: 649-671.

63. Furth, J. A., and Lorenz, E. 1954. Carcinogenesis by ionizing radiations. In vol. 1, *Radiation Biology,* edited by A. Hollaender, 145-201. New York: McGraw-Hill.

64. Marie, P.; Clunet, J.; and Raoulet-Lapointe, G. 1910. Contribution a l'etude du developement des tumeurs malignes sur les ulceres de roentgen. *Bull. de l'Assoc. Franc. pour l'Etude du Cancer* 3: 404-426.

65. Weinstein, I. B.; Gattoni-Celli, S.; Kirschmeir, P.; Lambert, M.; Hsiao, W.; Backer, J.; and Jeffrey, A. 1984. Multistage carcinogenesis involves multiple genes and multiple mechanisms. *J. Cell. Physiol.* (Suppl.) 3: 127-137.

66. Chaganti, R. S. K., and Jhanwar, S. C. 1983. Oncogenes, chromosome mutation, and the development of neoplasia. In *Chromosome Mutation and Neoplasia,* 397-412. New York: Alan R. Liss, Inc.

67. Temin, H. M. 1984. Do we understand the genetic mechanisms of oncogenesis. *J. Cell. Physiol.* (Suppl.) 3: 1-11.

68. Ford, C. E., and Clarke, C. M. 1963. Cytogenetic evidence of clonal proliferation in primary reticular neoplasms. *Can. Cancer Conf.* 5: 129-146.

69. Chaganti, R. S. K. The significance of chromosome change to neoplastic development. In reference 66, 359-396.

70. Fialkow, P. J. 1977. Clonal origin and stem cell evolution of human tumors. In *Genetics of Human Cancer*, edited by J. J. Mulvihill, R. W. Miller, and J. F. Fraumeni, Jr., 439-453. New York: Raven Press.

71. Fialkow, P. J.; Gartler, S. M.; and Yoshida, A. 1967. Clonal origin of chronic myelocytic leukemia in man. *Proc. Natl. Acad. Sci. USA* 58: 1468-1471.

72. National Toxicology Program. 1985. *Fourth annual report on carcinogens. Summary 1985* [NTP 85-002]. Washington, DC: Department of Health and Human Services.

73. Doll, R., and Peto, A. 1981. Avoidable risks of cancer in the U.S. *JNCI* 66: 1196-1308.

74. Waterhouse, J.; Muir C.; Correa, P.; and Powell, J., eds. 1976. *Cancer incidence in five continents* [IARC Sci Publications #15], vol. 3, 1-584. Lyon, France: International Agency for Research on Cancer.

75. Layton, J.; Warzynski, M.; and Idiris, A. 1986. Acquired immunodeficiency syndrome in the United States: A selected review. *Crit. Care Med.* 14: 819-827.

76. Chang, E. H.; Pirollo, K. F.; Zou, Z. Q.; Cheung, H.-Y.; Lawler, E. L.; Garner, R.; White, E.; Bernstein, W. B.; Fraumeni, J. W., Jr.; and Blattner, W. A. 1987. Oncogenes in radioresistant, noncancerous skin fibroblasts from a cancer-prone family. *Science* 237: 1036-1038.

77. Croce, C. M. 1987. Role of chromosome translocations in human neoplasia. *Cell* 49: 155-156.

78. Marshall, C. J. 1987. Oncogenes and growth control: 1987. *Cell* 49: 723-725.

79. Weinberg, R. A. 1985. The action of oncogenes in the cytoplasm and nucleus. *Science* 230: 770-776.

80. Bister, K., and Jansen, H. W. 1986. Oncogenes in retroviruses and cells: Biochemistry and molecular genetics. *Advances in Cancer Res.* 47: 99-188.

81. Antoniodes, H. N.; Pantazis, P.; and Owen, A. J. 1987. Human platelet-derived factor and the sis-PDGF-2 gene. In *Oncogenes, Genes, and Growth Factors,* edited by G. Guroff, 1-40. New York: John Wiley and Sons.

82. Klein, G., and Klein, E. 1987. Myc/Ig juxtaposition by chromosomal translocations: Some new insights, puzzles, and paradoxes. In *Oncogenes and Growth Factors,* edited by R. A. Bradshaw and S. Prentis, 33-46. New York: Elsevier Science Publishers.

83. Gilman, A. G. 1984. G proteins and dual control of adenylate cyclase. *Cell* 36: 577-579.

84. Forrester, K.; Almoguera, C.; Han, K.; Grizzle, W. E.; and Perucho, M. 1987. Detection of high incidence of K-ras oncogenes during human colon tumorigenesis. *Nature* 327: 298-303.

85. Jaffe, D. R., and Bowden, G. T. 1987. Enhanced malignant progression of mouse skin tumors by ionizing radiation and activation of oncogenes in radiation induced tumors. In vol. 1, *Proceedings of 8th International Congress of Radiation Research,* edited by E. M. Fielden, J. F. Fowler, J. H. Hendry, and D. Scott, 188. London: Taylor and Francis.

86. Sawey, M. J.; Burns, F. J.; and Garte, S. J. Activation of multiple oncogenes in radiation-induced rat skin carcinomas. In reference 85, 188.

87. Guerrero, L; Villasante, A.; Corces, V.; and Pellicer, A. 1984. Activation of a c-k-ras oncogene by somatic mutation in mouse lymphomas induced by gamma radiation. *Science* 225: 1159-1162.

88. Kudson, A. G., Jr. 1985. Hereditary cancer, oncogenes, and antioncogenes. *Cancer Res.* 45: 1437-1443.

89. Sager, A. 1986. Genetic suppression of tumor formation: A new frontier in cancer research. *Cancer Res.* 46: 1573-1580.

90. Harris, H. 1979. Some thoughts about genetics, differentiation, and malignancy. *Somatic Cell Mol. Genet*. 5: 923-930.

91. Kasid, U.; Pfeifer, A.; Weischelbaum, R. R.; Dritschilo, A.; and Mark, G. E. 1987. The raf oncogene is associated with a radiation-resistant human laryngeal cancer. *Science* 237: 1039-1041.

92. Dalla-Favera, R.; Bregni, M.; Erikson, J.; Patterson, D.; Gallo, R. C.; and Croce, C. M. 1982. Human c-myc oncogene is located on the region of chromosome 8 that is translocated in Burkitt's lymphoma cells. *Proc. Natl. Acad. Sci. USA* 79: 7824-7827.

93. Prakash, K.; McBride, O. W.; Swan, D. C; Devare, S. G.; Tronick, S. R.; and Aaronson, S. A. 1982. Molecular cloning and chromosomal mapping of a human locus related to the transforming gene of Moloney murine sarcoma virus. *Proc. Natl. Acad. Sci. USA* 79: 5210-5214.

94. Nowell, P. C., and Hungerford, D. A. 1960. A minute chromosome in chronic granulocytic leukemia. *Science* 132: 1497.

95. de Klein, A.; Geurts van Kessel, D. A.; Grosveld, G.; Bartrum, C. R.; Hagemeirer, A.; Bootsma, D.; Spurr, N. K.; Heisterkamp, N.; Groffen, J.; and Stephenson, J. R. 1982. A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukemia. *Nature* 300: 765-767.

96. Goffen, J.; Stephenson, J. K.; Heisterkamp, N.; de Klein, A.; Bartrum, C. R.; and Grosveld, G. 1984. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. *Cell* 36: 93-99.

97. Konopka, J. B.; Watanabe, S. M.; and White, O. N. 1984. An alteration of the human c-abl protein in K562 leukemia cells unmasks associated tyrosine kinase activity. *Cell* 37: 1035-1042.

98. Bishop, J. M. 1987. The molecular genetics of cancer. *Science* 235: 305-311.

99. Cairns, J. 1975. Mutational selection and the natural history of cancer. *Nature* 255: 197-200.

100. Mossman, K. V. 1984. Ionizing radiation and cancer. *Cancer Invest*. 2(4): 301-310.

101. Upton, A. C. 1983. Environmental standards for ionizing radiation: Theoretical basis for dose-response curves. *Environ. Health Perspect*. 52: 31-39.

102. Land, C. E. 1980. Estimating cancer risks from low doses of ionizing radiation. *Science* 209: 1197-1203.

103. Jablon, S. Epidemiologic perspectives in radiation carcinogenesis. In reference 50, 1-8.

104. Robinette, C. D.; Jablon, S.; and Preston, T. L. 1985. *Mortality of nuclear weapons test participants.* Washington, DC: National Research Council.

105. Preston, D. L.; Kato, H.; Kopecky, K. J.; and Fujita, S. 1987. Studies of mortality of A-bomb survivors. 8. Cancer mortality, 1950-1982. *Radiat. Res*. 111: 151-178.

106. Neel, J. V.; Satoh, C.; Hamilton, H. B.; Otake, M.; Goriki, K.; Kageoka, T.; Fujita, M.; Neriishi, S.; and Asakawa, J. 1980. Search for mutations affecting protein structure in children of atomic bomb survivors: Preliminary report. *Proc. Natl. Acad. Sci. USA* 77: 4221-4225.

107. Auxier, J. A. 1977. *Ichiban, radiation dosimetry for the survivors of the bombings of Hiroshima and Nagasaki* [ERDA Critical Review Series, TID-27080]. Springfield, VA: National Technical Information Service.

108. U.S.-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. 1987. In vol. 1, *Final report* [DS86, Dosimetry System 1986], edited by W. C. Roesch. Hiroshima: Radiation Effects Research Foundation.

109. Court Brown, W. M., and Doll, R. 1965. Mortality from cancer and other causes after radiotherapy for ankylosing spondilitis. *Br. J. Med.* 2: 1327-1332.

110. Smith, P. G. Late effects of X-ray treatment of ankylosing spondilitis. In reference 50, 107-118.

111. Smith, P. G., and Doll, R. 1982. Mortality among patients with ankylosing spondilitis after a single treatment course with X-rays. *Br. Med. J.* 284: 449-460.

112. Shore, R. E.; Albert, R. E.; and Pasternack, B. S. 1976. Follow-up study of patients treated by X-ray epilation for tinea capitis. *Arch. Environ. Health* 31: 17-28.

113. Shore, R. E.; Hemplemann, L. H.; Kowaluk, E.; Mansur, P. S.; Pasternack, B. S.; Albert, R. E.; and Haughie, G. E. 1977. Breast neoplasms in women treated with X-rays for acute postpartum mastitis. *JNCI* 59: 813-822.

114. Boice, J. D., and Monson, R. R. 1977. Breast cancer in women after repeated fluoroscopic examinations of the chest. *JNCI* 59: 823-832.

115. Boice, J. D., Jr.; Rosenstein, M.; and Trout, E. D. 1978. Estimation of breast doses and breast cancer risks associated with repeated fluoroscopic chest examinations of women with tuberculosis. *Radiat. Res.* 73: 373-390.

116. Waxweiler, R. J.; Roscoe, R. J.; Archer, V. E.; Thun, M. J.; Wagoner, J. K.; and Lundin, F. E., Jr. 1981. Mortality follow-up through 1977 of the white underground uranium miners cohort examined by the United States Public Health Service. In *Radiation Hazards in Mining,* 823-830. New York: Society of Mining Engineers.

117. Kunz, E.; Sevc, J.; Placek, V.; and Horacek, J. 1979. Lung cancer in man in relation to different time distribution of radiation exposure. *Health Phys*. 36: 699-706.

118. Ichimaru, M.; Ishimaru, L; Belsky, J. L.; Tomiyasu, T.; Sadamori, N.; Hoshino, T.; Tomonaga, M.; Shimizu, N.; and Okada, H. 1976. *Incidence of leukemia in atomic bomb survivors, Hiroshima and Nagasaki 1950-71*, *by radiation dose, years after exposure, age, and type of leukemia* [Technical Report RERF 10-76]. Hiroshima: Radiation Effects Research Foundation.

119. Clark, S. S.; McLaughlin, J.; Crist, W. M.; Champion, R.; and White, O. N. 1987. Unique forms of the abl tyrosine kinase distinguish Phl-positive CML from Phl-positive ALL. *Science* 235: 85-88.

120. Kato, H., and Schull, W. J. 1982. Studies of the mortality of A-bomb survivors. Report 7. Mortality, 1950-1978: Part I. Cancer mortality. *Radiat. Res.* 90: 395-432.

121. Smith, P. G., and Doll, R. 1976. Late effects of X irradiation in patients treated for metropathia haemorrhagica. *Br. J. Radiol*. 49: 224-232.

122. Straume, T., and Dobson, R. L. 1981. Implications of new Hiroshima and Nagasaki dose estimates: Cancer risks and neutron RBE. *Health Phys*. 41: 666-671.

123. Nuclear Regulatory Commission. 1983. *Radiation dose standards for individuals in restricted areas* [Code of Federal Regulations. Energy. Title 10, Part 20.101], 235. Washington, DC: Office of the Federal Register.

124. Center for Disease Control. 1979. Leukemia among persons present at an atmospheric nuclear test (SMOKY). *MMWR* 28: 361-362.

125. Caldwell, G. G.; Kelley, D. B.; and Heath, C. W. 1980. Leukemia among participants in military maneuvers at a nuclear bomb test. A preliminary report. *JAMA* 244: 1575-1578.

126. Caldwell, G. G.; Kelley, D. B.; Zack, M.; Falk, H.; and Heath, C. 1983. Mortality and cancer frequency among military nuclear test (SMOKY) participants, 1957 through 1979. *JAMA* 250: 620-624 .

127. Ron, E., and Modan, B. 1980. Benign and malignant thyroid neoplasms after childhood irradiation for tinea capitis. *JNCI* 65: 7-11.

128. Hemplemann, L. H.; Hall, W. J.; Phillips, M.; Cooper, R. A.; and Ames, W. R. 1975. Neoplasms in persons treated with X-rays in infancy: Fourth survey in 20 years. *JNCI* 55: 519-530.

129. Prentice, R. L.; Kato, H.; Yoshimoto, K.; and Mason, M. 1982. Radiation exposures and thyroid cancer incidence among Hiroshima and Nagasaki residents. In *Third Symposium on Epidemiology and Cancer Registries in the Pacific Basin* [National Cancer Institute Monograph 62], 207-212. Washington, DC: Government Printing Office.

130. Wood, J. W.; Tamagaki, H.; Neriishi, S.; Sato, T.; Sheldon, W. F.; Archer, P. G.; Hamilton, H. B.; and Johnson, K. G. 1969. Thyroid carcinoma in atomic bomb survivors, Hiroshima and Nagasaki. *Am. J. Epidemiol.* 89: 4-14.

131. McTierman, M. M.; Weiss, N. S.; and Daling, J. R. 1984. Incidence of thyroid cancer in women in relation to previous exposure to radiation therapy and history of thyroid disease. *JNCl* 73: 575-581.

132. Shore, R. E.; Woodard, E; Hildreth, N.; Dvoretsky P.; Hemplemann, L.; and Pasternack B., 1985. Thyroid tumors following thymus irradiation. *JNCI* 74: 1117-1184.

133. Doniach, I. 1974. Carcinogenic effect of 100, 250, and 500 rad X-rays on the rat thyroid gland. *Br. J. Cancer* 30: 487-495.

134. Conard, R. A.; Paglia, D. E.; Narsen, P. R.; Sutlow, W.W.; Dobyns, B. M.; Robins, J.; Krotsky, W. A.; Field, J. B.; Rall, J. E.; and Wolff, J. 1980. *Review of medical findings in a Marshallese population twenty-six years after accidental exposure to radioactive fallout* [Brookhaven National Laboratory Report BNL 51261]. Springfield, VA: National Technical Information Service.

135. Ron, E., and Modan, B. Thyroid and other neoplasms following childhood scalp irradiation. In reference 50, 139-151.

136. Modan, B.; Ron, E.; and Werner, A. 1977. Thyroid cancer following scalp irradiation. *Radiology* 123: 741-744.

137. National Council on Radiation Protection and Measurements. 1977. *Protection of the thyroid gland in the event of releases of radioiodine* [NCRP Report 55]. Washington, DC: National Council on Radiation Protection and Measurement.

138. Howe, G. R. Epidemiology of radiogenic breast cancer. In reference 50, 119-129.

139. Seidman, H., and Mushinski, M. H. 1983. Breast cancer: Incidence, mortality, survival, and prognosis. In *Breast Carcinoma. Current Diagnosis and Treatment,* edited by S. A. Feig and R. McLelland, 9-46. New York: Masson Publishing USA, Inc.

140. Tokunaga, M.; Land, C. E.; Yamamoto, T.; Masahide, A.; Tokuoka, S.; Ezaki, H.; Nishimori, L; and Fujikura, T. Breast cancer among atomic bomb survivors. In reference 50, 45-55.

141. Orine, S. K.; Chambers, R. W.; and Johnson, R. H. 1967. Postirradiation carcinoma of the male breast bilaterally. *JAMA* 201: 707
.
142. Boice, J. D., Jr.; Land, C. E.; Shore, R. E.; Norman, J. E.; and Tokunaga, M. 1979. Risk of breast cancer following low-dose exposure. *Radiology* 131: 589-597.

143. Tokunaga, M.; Land, C. E.; Yamamoto, T.; Asano, M.; Tokuoka, S.; Ezaki, H.; and Nishimori, I. 1982. Breast cancer in Japanese A-bomb survivors. *Lancet* 2: 924.

144. Tokunaga, M.; Norman, N. E., Jr., Asano, M.; Tokuoka, S.; Ezaki, H.; Nishimori, L; and Tsuju, Y. 1979. Malignant breast tumors among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1974. *JNCI* 62: 1347-1359.

145. Hildreth, N. G.; Shore, R. E.; and Hemplemann, L. H. 1983. Risk of breast cancer among women receiving radiation treatment in infancy for thymic enlargement. *Lancet* 2: 273.

146. Land, C. E.; Boice, J. D., Jr.; Shore, R. E.; Norman, J. E.; and Tokunaga, M. 1980. Breast cancer risks from low-dose exposures to ionizing radiation: Results of parallel analysis of three exposed populations of women. *JNCI* 65: 353-376.

147. Davis, F. G.; Boice, J. D., Jr.; Kelsey, J. L.; and Monson, R. R. 1987. Cancer mortality after multiple fluoroscopic examinations of the chest. *JNCI* 78: 645-652.

148. Rowland, R. E., and Lucas, H. F. Radium-dial workers. In reference 50, 231-240.

149. Adams, E. E., and Brues, A. M. 1980. Breast cancer in female radium dial workers first employed before 1930. *J. Occup. Med*. 22: 583-587.

150. Modan, B.; Baidatz, D.; Mart, H.; Steintz, R.; and Levin, S. 1969. Radiation-induced intracranial meningiomas. *Clin. Radial*. 20: 90-94.

151. Shore, R. E.; Albert, R. E.; and Pasternack, B. S. 1976. Followup study of patients treated by x-ray epilation for tinea capitis. Resurvey of post-treatment illness and mortality experience. *Arch. Environ. Health* 31: 17-28

152. Asano, M.; Kato, H.; Yoshimoto, K.; Seyama, S.; Itakura, H.; Hamada, T.; and Iijima, S. 1982. Primary liver carcinoma and liver cirrhosis in atomic bomb survivors, Hiroshima and Nagasaki, 1961-75, with special reference to hepatitis B surface antigen. *JNCI* 69: 1221-1227.

153. Lewin, K., and Millis, R. R. 1973. Radiation hepatitis: A morphologic study with emphasis on the late changes. *Arch. Pathol*. 96: 21-26.

154. Prentice, R. L.; Yoshimoto, Y.; and Mason, W. W. 1983. Relationship of cigarette smoking and radiation exposure to cancer mortality in Hiroshima and Nagasaki. *JNCI* 70: 611-622.

155. Little, J. B.; Radford, E. P.; McCombs, H. L.; and Hunt, V. R. 1965. Distribution of polonium-210 in pulmonary tissues of cigarette smokers. *N. Eng. J. Med*. 273: 1343-1351.

156. Winters, T. H., and Di Franza, J. R. 1982. Radioactivity in cigarette smoke. *N. Eng. J. Med.* 306: 364-365.

157. Radford, E. P., and Hunt, V. R. 1964. Polonium-210: A volatile radioactive element in cigarettes. *Science* 143: 247-249.

158. Little, J. B.; McGandy, R. B.; and Kennedy, A. R. 1978. Interactions between polonium-210, alpha-radiation, benzo(a)pyrene, and 0.9% NaCl solution instillations in the induction of experimental lung cancer. *Cancer Res.* 38: 1929-1935.

159. Wynder, E. L., and Hoffman, D. 1979. Tobacco and health: A societal challenge. *N. Eng. J. Med.* 300: 894-903.

160. Van Dyk, J.; Keane, T. J.; Kan, S.; Rider, W. D.; and Fryer, C. J. H. 1981. Radiation pneumonitis following large single dose irradiation: A re-evaluation based on absolute dose to lung. *Int. J. Radial. Oncol. Biol. Phys.* 7: 461-467.

161. Gross, N. J. 1977. Pulmonary effects of radiation therapy. *Ann. Intern. Med.* 86: 81-92.

162. Tokuoka, S.; Kawai, K.; Shimizu, Y.; Inai, K.; Ohe, K.; Fujikura, T.; and Kato, H. 1987. Malignant and benign ovarian neoplasms among bomb survivors, Hiroshima and Nagasaki, 1950-80. *JNCI* 79: 47-57.

163. Muller, H. J. 1927. Artificial transmutation of the gene. *Science* 66: 84-87.

164. Muller, H. J. The nature of the genetic effects produced by radiation. In reference 63, 351-474.

165. Denniston, C. 1982. Low level radiation and genetic risk estimation in man. *Annu. Rev. Genet.* 16: 329-355.

166. Russell, W. L., and Kelly, E. M. 1982. Mutational frequencies in male mice and the estimation of genetic hazards of radiation in men. *Proc. Natl. Acad. Sci. USA* 79: 542-544.

167. Selby, P. B., and Selby, P. R. 1977. Gamma-ray-induced dominant mutations that cause skeletal abnormalities in mice. *Mutat. Res.* 43: 907-975.

168. Searle, T. 1987. Radiation—the genetic risk. *Trends Genet.* 3: 152-157.

169. Abrahamson, S. 1979. Genetic effects of low level radiation. In *Proceedings of a Conference: Known Effects of Low-Level Radiation Exposure. Health Implications of the TMI Accident* [NIH Publication 80-2087], 46-60. Washington, DC: U.S. Department of Health, Education, and Welfare.

170. Popescu, H. L.; Pilat, L.; Hilt, M.; and Lancranjan, I. 1972. Evolution of biological changes noticed in three cases of accidental mild gamma irradiation. *J. Occup. Med.* 14: 317-320.

171. Dolphin, G. W.; Bolton, D.; Humphreys, D. L. O.; Speight, D. L.; and Stradling, G. N. 1970. Biological dosimetry and physical dosimetry after a radiation accident. *Nature* 227: 165.

172. Randolph, M. L., and Brewer, J. G. 1980. Estimation of whole-body doses by means of chromosome aberrations observed in survivors of the Hiroshima A-bomb. *Radiat. Res.* 82: 393-407.

173. Cohen, B. L. 1984. Perspective on genetic effects of radiation. *Health Phys.* 46: 1113-1121.

174. Strauss, B. S. 1985. Cellular aspects of DNA repair. *Adv. Cancer Res.* 45: 45-105.

175. Ward, J. F. 1975. Molecular mechanisms of radiation-induced damage to nucleic acids. *Adv. Radiat. Biol.* 5: 181-239.

176. Hook, E. B. 1981. Rates of chromosome abnormalities in different maternal ages. *Obstet. Gynecol.* 58: 282-285.

177. Freidman, J. M. 1981. Genetic disease in the offspring of older fathers. *Obstet. Gynecol.* 57: 745-749.

178. National Council on Radiation Protection and Measurements. 1979. *Tritium and other radionuclide labeled organic compounds incorporated in genetic material* [NCRP Report 63]. Washington, DC: National Council on Radiation Protection and Measurements.

179. National Council on Radiation Protection and Measurements. 1987. *Genetic effects from internally deposited radionuclides* [NCRD Report 89]. Washington, DC: National Council on Radiation Protection and Measurement.

180. Jablon, S., and Kato, H. 1971. Sex ratio in offspring survivors exposed prenatally to the atomic bombs in Hiroshima and Hagasaki. *Am. J. Epidemiol*. 93: 253-258.

181. Sigler, A. T.; Lilienfield, A. M.; Cohen, B. H.; and Westlake, J. E. 1965. Radiation exposure in parents of children with mongolism (Down's syndrome). *Bull. Hopkins Hosp.* 117: 374-399.

182. Uchida, I. A., and Curtis, E. J. 1961. A possible association between maternal irradiation and mongolism. *Lancet* 2: 845-850.

183. Uchida, I. A.; Holunga, R.; and Lawler, C. 1968. Maternal radiation and chromosomal aberrations. *Lancet* 2: 1045-1049.

184. Alberman, E.; Polani, P. E.; Roberts, J. A. F.; Spicer, C. C.; Elliot, M.; and Armstrong, E. 1972. Paternal exposure to X-irradiation and Down's syndrome. *Ann. Hum. Genet*. 36: 195-208.

185. Schull, W. J.; Otake, M.; and Neel, J. V. 1981. Genetic effects of the atomic bomb: A reappraisal. *Science* 213: 1220-1227.

186. Brewen, J. G.; Preston, R. J.; and Gengozian, N. 1975. Analysis of X-ray induced translocations in human and marmoset spermatogonial stem cells. *Nature* 253: 468-470.

187. Oftedal, P., and Searle, A. G. 1980. An overall genetic risk assessment for radiological protection purposes. *J. Med. Genet.* 17: 15-20.

188. Russell, L. B. 1950. X-ray induced development abnormalities in the mouse and their use in the analysis of embryological patterns. I. External and gross visceral changes. *J. Exp. Zool.* 114: 545-602.

189. Rugh, R. 1962. Ionizing radiations and congenital anomalies of the nervous system. *Mil. Med.* 127: 883-907.

190. Rugh, R. 1964. Why radiobiology? *Radiology* 82: 917-920.

191. Russell, L. B., and Russell, W. L. 1952. Radiation hazards to the embryo and fetus. *Radiology* 58: 369-376.

192. Rugh, R. 1971. X-ray induced teratogenesis in the mouse and its possible significance to man. *Radiology* 99: 433-443.

193. Yamazaki, J. 1966. A review of the literature on the radiation dosage required to cause manifest central nervous system disturbances from *in utero* and postnatal exposure. *Pediatrics* 37: 977-1003.

194. Russell, L. B., and Russell, W. L. 1954. An analysis of the changing radiation response of the developing mouse embryo. *J. Cell Comp. Physiol*. 43: 103-149.

195. Rugh, R., and Grupp, E. 1959. Response of the very early mouse embryo to low levels of ionizing radiations. *J. Exp. Zool.* 141: 571-587.

196. Russell, L. B. 1956. X-ray induced developmental abnormalities in the mouse, and their use in analysis of embryological patterns. II. Abnormalities of the vertebral column and thorax. *J. Exp. Zool.* 131: 329-395.

197. Ohzu, E. 1965. Effects of low dose X-irradiation on early mouse embryos. *Radiat. Res.* 26: 107-113.

198. Rugh, R. 1969. Low dose X-ray effects on the precleavage mammalian zygote. *Radiat. Res.* 37: 401-414.

199. Russell, L. B., and Montgomery, C. S. 1966. Radiation-sensitivity differences within cell-division cycles during mouse cleavage. *Int. J. Radiat. Biol.* 10: 151-164.

200. Jacobson, L. 1968. *Low-dose X-irradiation and teratogenesis: A quantitative experimental study with reference to seasonal influence on dose effects.* Copenhagen: Munksgaard.

201. Miller, R. W., and Mulvihill, J. J. 1976. Small head size after atomic irradiation. *Teratology* 14: 355-358.

202. Dobson, R. L.; Koehler, C. G.; Felton, J. S.; Kwan, T. C.; Wuebbles, B. J.; and Jones, D. C. L. 1978. Vulnerability of female germ cells in developing mice and monkeys to tritium, gamma rays, and polycyclic hydrocarbons. In *Development Toxicology of Energy-Related Pollutants. Proceedings of 17th Annual Hanford Biology Symposium* [CONF-771017], 1-14. Washington, DC: U.S. Department of Energy Symposium Series.

203. Lebedinsky, A. V.; Grigoryev, U. G.; and Demirchoglyan, G. G. 1958. The biological effects of small doses of ionizing radiation. [The cited work was done by V. V. Yokolev.] In *Proceedings of Second United Nations International Conference on the Peaceful Uses of Atomic Energy*. Vol. 22, *Biological Effects of Radiation,* 26. New York: United Nations Publications.

204. Brent, R. L. 1960. The effect of irradiation on the mammalian fetus. *Clin. Obst. Gynecol*. 3: 928-950.

205. Semagin, V.N. 1964. Higher nervous activity of adult rats irradiated daily with X-rays during the embryonic period. In *Effects of Ionizing Radiation on the Functions of Higher Nervous System of Progeny*, edited by I. A. Pintsovskoyo and translated by the U.S. Atomic Energy Commission [AEC-TR-5553], 77-103. Oak Ridge, TN: U.S. Atomic Energy Commission.

206. Cahill, D. F., and Yuile, C. L. 1970. Tritium. Some effects of continuous exposure *in utero* on mammalian development. *Radiat. Res*. 44: 727-737.

207. Bursian, S. J.; Cahill, D. F.; and Laskey, J. W. 1975. Some aspects of brain neurochemistry after intrauterine exposure to tritium. *Int. J. Radiat. Biol*. 27: 455-461.

208. Kaplan, S. 1962. Behavioral manifestations of the deleterious effects of prenatal X-irradiation. In *Effects of Ionizing Radiation on the Nervous System*, 225-243. Vienna: International Atomic Energy Agency.

209. Rugh, R., and Grupp, E. 1960. Fractionated X-irradiation of the mammalian embryo and congenital anomalies. *Am. J. Roentgenol*. 84: 125-144.

210. Russell, L. B.; Badgett, S. K.; and Saylors, C. L. 1960. Comparison of the effects of acute continuous and fractionated irradiation during embryonic development. In *Immediate and Loin-Level Effects of Ionizing Radiation,* proceedings of a conference held in Venice [Special Supplement to *Int. J. Radiat. Biol.*], 343-359. London: Taylor and Francis.

211. Krigel, H., and Reihart, S. 1969. Effect of a fractionated X-irradiation of the development of the mammalian fetus. In *Radiation Biology of the Fetal and Juvenile Mammal*, edited by M. R. Sikov and D. D. Mahlum, 251-262. Washington, DC: U.S. Atomic Energy Commission, Division of Technical Information.

212. Grahn, D., and Kratchman, J. 1963. Variation in neonatal death rate and birth weight in the United States and possible relations to environmental radiation, geology and altitude. *Am. J. Hum. Genet.* 15: 329-352.

213. Hickey, R. J.; Bowers, E. J.; Spence, D. E.; Zemel, B. S.; Clelland, A. B.; and Clelland, R. C. 1981. Low level ionizing radiation and human mortality: Multi-regional studies. A preliminary report. *Health Phys*. 40: 625-641.

214. Jacobsen, L. Radiation-induced teratogenesis in relation to season and some features of reproductive biology. In reference 211, 229-242.

215. Taylor, A. I. 1968. Autosomal trisomy syndromes: A detailed study of 27 cases of Edward's Syndrome and 27 cases of Patau's Syndrome. *J. Med. Genet.* 5: 227-252.

216. Murphree, R. L., and Graves, R. B. Effect of dose rate on prenatally irradiated lambs. In reference 211, 243-250.

217. Rugh, R. Chairman's remarks. In reference 211, 381-391.

218. Friedberg, W.; Hanneman, G. D.; Faulkner, D. N.; Darden, E. B., Jr.; and Deal, R. B., Jr. 1973. Prenatal survival of mice irradiated with fission neutrons or 300 kVp X-rays during the pro-nuclear-zygote stage: Survival curves, effects of dose fractionation. *Int. J. Radiat. Biol.* 24: 549-560.

219. Brent, R. L., and Bolden, B. T. 1968. Indirect effect of X-irradiation on embryonic development: Utilization of high doses of maternal irradiation on the first day of gestation. *Radiat. Res*. 36: 563-570.

220. Brent, R. L., and Bolden, B. T. 1967. The indirect effect of irradiation on embryonic development. III. The contribution of ovarian irradiation, uterine irradiation, oviduct irradiation, and zygote irradiation to fetal mortality and growth retardation in the rat. *Radiat. Res.* 30: 759-773.

221. Brent, R. L., and McLaughlin, M. M. 1960. The indirect effect of irradiation on embryonic development. I. Irradiation of the mother while shielding the embryonic site. *Am. J. Dis. Child* 100: 94-102.

222. Hicks, S. P., and D'Amatio, C. J. 1963. Low dose radiation of the developing brain. *Science* 141: 903-905.

223. Wood, J. W.; Johnson, K. G.; and Omori, Y. 1967. *In utero* exposure to the Hiroshima atomic bomb. An evaluation of head size and mental retardation: 20 years later. *Pediatrics* 39: 385-392.

224. Brent, R. Radiation effects on the developing embryo. In reference 169, 61-75.

225. National Council on Radiation Protection and Measurement. 1977. *Medical radiation exposure of pregnant and potentially pregnant women* [NCRP Report

54]. Washington, DC: National Council on Radiation Protection and Measurement.

226. National Council on Radiation Protection and Measurement. 1977. *Review of NCRP radiation dose limit for embryo and fetus in occupationally-exposed women* [NCRP Report 53]. Washington, DC: National Council on Radiation Protection and Measurement.

227. Dekaban, A. S. 1968. Abnormalities in children exposed to X-irradiation during various stages of gestation: Tentative timetable of radiation injury to human fetus. *J. Nucl. Med.* 9: 471-477.

228. Goldstein, L., and Murphy, D. P. 1929. Etiology of ill-health in children born after postconceptional maternal irradiation. *Am. J. Roentgenol.* 22: 322-331.

229. Goldstein, L., and Murphy, D. P. 1929. Microcephalic idiocy following radium therapy for uterine cancer during pregnancy. *Amer. J. Obstet. Gyneco*l. 18: 189-195, 281-283.

230. Jacobsen, L., and Mellemgaard, L. 1968. Anomalies of the eyes in descendants of women irradiated with small X-ray doses during the age of fertility. *Acta Ophthalmol*. 46: 352-354.

231. Yamazaki, J.; Wright, S.; and Wright, P. 1954. Outcome of pregnancy in women exposed to the atomic bomb in Nagasaki. *Am. J. Dis. Child* 82: 448-463.

232. Blot, W. J. 1975. Growth and development following prenatal exposure and childhood exposure to atomic radiation. *Radiat. Res*. (Suppl.) 16: 82-88.

233. Blot, W. J., and Miller, R. J. 1973. Mental retardation following *in utero* exposure to the atomic bombs of Hiroshima and Nagasaki. *Radiology* 106: 617-619.

234. Ishimaru, T.; Nakashima, E.; and Kawamoto, S. 1985. *Relationship of height, body weight, head circumference, and chest circumference at age 18, to gamma and neutron doses among in utero exposed children, Hiroshima and Nagasaki* [Technical Report RERF TR 19-84]. Hiroshima: Radiation Effects Research Foundation.

235. Kallinger, W., and Granniger, W. 1979. The effect of a high gamma dose on a human fetus. *Health Phys*. 36:1-6.

236. Griem, M. L.; Mewissen, D. J.; Meier, P.; and Dobben, G. D. Analysis of the morbidity and mortality of children irradiated in fetal life. In reference 211, 651-659.

237. Harris, W. 1932. Therapeutic abortion produced by the roentgen ray. *Am. J. Roentgenol*. 27: 415-419.

238. Mayer, M. D.; Harris, W.; and Wimpfheimer, S. 1936. Therapeutic abortion by means of X-ray. *Am. J. Obstet. Gynecol.* 32: 945-957.

239. Stewart, A. M.; Webb, J. W.; Giles, B. D.; and Hewitt, D. 1956. Malignant disease in childhood and diagnostic irradiation *in utero. Lancet* 2: 447, 1956.

240. Stewart, A. M.; Webb, J. W.; and Hewitt, D. 1958. A survey of childhood malignancies. *Br. Med. J.* 1: 1495-1508.

241. Stewart, A. M., and Kneale, G. W. 1970. Radiation dose effects in relation to obstetric X-rays and childhood cancers. *Lancet* 1: 1185-1188.

242. Kneale, G. W., and Stewart, A. M. 1976. Mantel-Haenszel analysis of Oxford data. II. Independent effects of fetal irradiation subfactors. *JNCI* 57: 1009-1014.

243. Monson, R. R., and MacMahon, B. Prenatal X-ray exposure and cancer in children. In reference 50, 97-105.

244. National Council on Radiation Protection and Measurement. 1987. *Recommendations on limits for exposure to ionizing radiation* [NCRP Report 91]. Washington, DC: National Council on Radiation Protection and Measurement.

245. Cohen, B. L., and Lee, I.-S. 1979. A catalog of risks. *Health Phys*. 36: 707-722.

246. National Council on Radiation Protection and Measurement. 1971. *Basic radiation protection criteria* [NCRP Report 39]. Washington, DC: National Council on Radiation Protection and Measurement.

247. Holahan, E. V., Jr. Cellular radiation biology. In reference 4, 87-110.

Return to Table of Contents